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Editorial

GRIPESMANSHIP: A POSITIVE APPROACH

In a recent issue of the weekly magazine published by the British Broadcasting Corporation, *The Listener*, a brilliant analysis of Soviet foreign trade began with a pertinent story about the Congress of Vienna. Metternich, on learning of the death of the chief Russian delegate, is supposed to have pondered deeply and then exclaimed, "Now, I wonder what his *motive* was?"

Concern about the motivation behind physical or verbal action, although by no means a modern phenomenon, seems to wax increasingly important in our time. Appropriately enough—since Freud provided strong fuel for the motivational bonfire—the question of *why* someone says something appears to bother psychiatrists and psychoanalysts excessively, but not exclusively.

In all cases, it may prove a pernicious preoccupation, since it often distracts attention from a more fundamental consideration, to wit: *Is there any merit in what is being said?* Nonetheless, let me quickly acknowledge the Goddess of Motivation and pay her my respects, if for no other reason than to focus the more sharply on content.

I am here, then, as one academic pharmacologist. I speak for no society, university, department, or agency. What I have to say will be said because I believe that the problems to be discussed are important, of some interest to this audience, and soluble. Evangelism and crusading are not my business; neither is the pondering of imponderables.

What I *am* concerned with is the amelioration of certain conditions which threaten to prevent clinical pharmacology from developing optimally. Since clinical pharmacology *is* my business, I am speaking from that most defensible, rational, and universal position—enlightened self-interest.

It is distressing to me that the exigencies of time prohibit my dwelling on the many pleasant aspects of relationships between medical schools and the drug industry. Those who know me best are well aware of the multiplicity of my

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own associations with industry and my continuing efforts to strengthen those ties. But past achievements in industry need no emphasis from me and I propose that mutual admiration might better be reserved for less hurried and more informal occasions.

My plan is to take up, in order, the following topics: (1) some sources of discontent with industry that are in large part justifiable by fact; (2) some complaints against industry that I consider unfair and unreasonable; (3) some serious problems facing not only the drug industry but the universities and the medical profession as well, deriving from the attitudes and activities of governmental agencies or bodies; (4) some general problems related to research in clinical pharmacology; (5) constructive suggestions for solving some of these problems; and (6) the irresponsibility of scientific journalism.

Let us begin then with what I consider some legitimate reasons for disenchantment with the pharmaceutical industry. (At the risk of sounding like the author of *Tristram Shandy*, I must digress for a moment. In this discussion I keep talking about the drug industry as a totality. I fear that in the minds of a large segment of the medical profession the industry *is* considered in monolithic terms. Criticisms are, it is true, sometimes directed specifically at one firm or another, but the brush of criticism is likely to tar all drug houses for the error of individual firms. This is unfortunate, just as it is unfortunate to categorically label all unions corrupt or all Hollywood marriages failures, but facts must be faced.)

Perhaps the major source of friction between the medical public—particularly the university circles—and the drug houses is sleazy advertising. Many physicians are upset by the fact that pharmaceutical promotion is not always as respectable as they would like it to be.

There are, for example, the badly scissored quotes—the utilization of only those parts of manuscripts or reports which laud the product and the elimination of less favorable comments or data. I realize that this is an old technique in advertising and certainly a classical technique in the theatre arts, but the special character and importance of products designed for improving the public health would seem to call for a higher level approach to advertising.

Then we have the "pharmaceutical numbers racket." We are told that a new compound is "more potent" than an older drug because the new agent works in doses of 10 mg., whereas the old requires 100 mg. What is usually meant is that at these doses both drugs do the same job and produce about the same incidence of untoward side reactions. Lacking some increase in quantitative effect, a decrease in toxicity, or a qualitative improvement of some sort, this situation becomes a matter of medical bookkeeping rather than therapeutic progress.

A more subtle problem is the circulation by drug houses of thousands of reprints of journal articles to the physicians of the country. Although I would not necessarily agree with the sentiment, many consider such action a reflection on the integrity of the author of the article, a form of unethical personal advertising, a sort of soul-selling in return for either financial gain or publicity. In my opinion such behavior on the part of authors of articles is strictly their own business. But I do see a point in the objection that work done at a famous

institution or clinic and published as such raises a different question, i.e., does the circulation of this kind of reprint represent an attempt to utilize for financial gain an institution's reputation?

Another source of complaints arises from certain unwise actions by detail men visiting physicians' offices. It appears to be considered fair game by some of these men to criticize sharply a competitor's product, advertising, honesty, or ethics. This approach lends itself, even when the points are well taken, to the interpretation that such activity is evidence of unscrupulousness and backbiting in the industry at large.

The employment of medical students during the summer as detail men of sorts for pharmaceutical firms has annoyed both deans and practicing physicians. The argument here is that it takes unfair advantage of the physician, who is naturally disposed to be friendly to the student and is therefore put in the difficult position of either appearing unfriendly or appearing susceptible to the manufacturer's approach.

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Some of these unhappy advertising techniques are readily admitted by many men in industry to be real and undesirable, although others persist in denying that errors of any consequence are ever committed by respectable firms. The medical public, let me assure you, is becoming increasingly convinced of the poor quality of certain drug advertising.

Anyone who tried to sample doctor response to the famous 1956 letter from an official of the National Association of Science Writers to the *Journal of the American Medical Association*, describing the devious publicity activities of one company, realizes the terrific impact even one such event can have.

A reaction of otherwise responsible pharmaceutical personnel which is especially annoying is the explicit admission of sleazy advertising coupled with the excuse that the fault lies with "those guys in the front office" or "the Madison Avenue boys." Without denying the possible truth of such statements one can take strong issue with the idea that they help the situation in any way. The abrogation of responsibility via the technique of buck-passing is rarely a satisfactory shield.

Let us now consider another formidable source of discontent for many physicians, academic and nonacademic—the avalance of "new" preparations threatening to bury the doctor each year. The hundreds of new names thus introduced pose a natural threat to the doctor's ability to assimilate new information.

What makes things worse is the realization by many physicians that most "new drugs" are merely combinations or new dosage formulations of old drugs and represent precious little in the way of therapeutic advance. The coexistence of anywhere from two to a half dozen or more medications in fixed ratio in the same capsule is in many instances poor medical practice, since the real need for simultaneous administration of multiple medicaments is usually overstated and the inflexibility of dosage imposed by drug combinations is a drawback when there *is* a need for the combination of two or more drugs. (For those of you who think that such criticism is indigenous to this country, incidentally, I can refer you to a blistering indictment last year against the German drug industry from a prominent German scientist.) It is again disappointing, in this regard, to see

respected drug firms following the path of least resistance. I have heard a pharmaceutical scientist attack a competitor's mixture as medicinal idiocy, only to confess that a similar preparation would soon be marketed by his own company because "we can't afford not to."

Another whole area of controversy has its origins in the great influence of the drug industry in support of new drug research. Manufacturers are understandably eager for success with an experimental drug; there is no "sweet smell" to failure. They are also understandably eager for a speedy answer. The scene is therefore set for pressure—conscious or unconscious, direct or indirect, subtle or flagrant—on the investigator to come up with the "right answer" in a hurry. Since clinical research is usually slow and rarely dramatic, it is easy to see how resentment can develop. Pressure can also arise in regard to recording results for publication, which is a considerably more serious problem.

A second difficulty in this area is the objection of most firms to nonproject-oriented support. The experienced investigator is just as anxious to maintain a nucleus of good people, both professional and nonprofessional, as is the pharmaceutical administrator. To do this efficiently he prefers smaller amounts of steady support to larger grants appearing erratically. He also wants to be able to pursue an exciting lead, even one without obvious commercial implications, if it arises in the course of clinical research, and he is naturally disappointed if a drug house withdraws support at this stage of an investigation.

A very thorny bit of controversy revolves about the risks attendant on the early evaluation of new drugs. Many clinical investigators rightly resent the medicolegal risks they run and are not eager to continue to "experiment at their own peril." They want industry to shoulder some of the responsibility and to at least sit down and discuss the malpractice coverage problem as it pertains to the investigators collecting the data for the pharmaceutical firm.

One final legitimate criticism from the direction of the universities is forthcoming. There is a good deal of banter exchanged between industrial and academic scientists about "freedom," salaries, working conditions, etc. But some of the banter is harsh and strident and generates ill will. I shall not defend the academicians for their role in this, for at the moment my job is to point the finger at industry.

The question here is the propriety (*and* accuracy) of the statements made by some pharmaceutical leaders that industry corrals most of the "professionals" sooner or later, leaving the "amateurs" (i.e., the duffers, second-raters, incompetents) in the universities. Besides being untrue—neither industry nor the medical schools have a monopoly on talent—this claim is in poor taste and hardly calculated to win friends.

Let me now quickly shift gears and briefly touch on some alleged sources of malcontent which I think are not based on fact. A shockingly off-base example was the recent resolution of the Association of American Medical Colleges criticizing certain activities of the drug industry. The Association apparently feels that cocktail parties, steak dinners, and awards of various sorts donated by industry to medical students, house staffs, and other groups are merely unscrupulous and subversive measures employed by drug houses to forward their nefarious plans.

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Such a statement could not have been made except from the abyss of almost total ignorance. It has been my experience that more often than not drug houses are asked, nay pressured, to provide food or drink at meetings of various sorts.

Certainly the criticism that a graduating honor student should not be allowed to accept a fine gold wristwatch because of the presence on its reverse side of an inscription indicating the donor seems the pinnacle of imbecility. (I must confess that the report did provide me with several minutes' worth of amusement, conjuring up as it did the vision of the hapless valedictorian removing his wristwatch periodically during the day to wave it guiltily about in the air so as to advertise the donor.) What the authors of this resolution seem to be rather clearly implying is that medical students and physicians are such dupes as to be easily converted by minor pleasantries into unwilling Trilbys hypnotized by drug-house Svengalis. The inevitable conclusion is that the medical profession is severely deficient in intelligence or integrity. I am more concerned with the inability of physicians to interpret advertising claims (which is *not* an easy trick) than with their willingness to trade their souls for a steak dinner!

I think it unreasonable also for some academicians to insist that most of the industry's funds for clinical investigation be allocated to nonproject-oriented grants. The drug companies admittedly have a lot that must be done in regard to specific compounds needing investigation and one can at best hope for only a small fraction of available funds to be directed to general support of continuing clinical pharmacologic programs in university clinics.

Similarly, I believe that investigators must be realistic and fair in acceding to the industry's reasonable requests for progress reports on new drugs. To keep data buried for 6 months to a year after it has been accumulated instead of reporting the results to the interested drug house seems cavalier action indeed.

Still another fanciful demand by certain individuals outside of industry, is that industry always behave like a nonprofit, altruistic organization. This quixotic request has perhaps been fostered by statements—ill-advised, in my opinion—by industrial leaders attempting to sell the idea that the primary concern of the drug houses is the welfare of the public.

This is not the *primary* concern of the drug industry, any more than it is the *primary* concern of the American Medical Association or the Chamber of Commerce. Do not mistake my meaning; I am *not* saying that the basic activities of these groups are incompatible with advancing the public welfare but merely that the two are not identical.

The point is beautifully made by a British firm, Vitamins, Ltd., in its advertisements. These take the form of an imaginary dialogue between a counsel for "the man in the street" and a pharmaceutical manufacturer. The counsel asks, in a voice which seems to be dripping venom, whether the public interest is "the lodestar of pharmaceutical firms," to which the manufacturer replies with candor and devastating effectiveness, "No more than it is for lawyers, say. Apart from such public spirit as we have, and the many controls that affect us, *what we do for the public good is a by-product of what we do for our own private good.*"

Let me now move on to some problems in the general area of governmental activities, first the Food and Drug Administration. A serious shortcoming of

the FDA is its inadequate budget, which is inescapably linked with its inability to attract top-drawer men in sufficient quantity. The FDA is too important, I suggest, for it to have any but the best men.

We should not ask that a few capable and dedicated scientists try to function without sufficient funds and adequate help, or with personnel of inferior caliber. There are other considerations besides funds here; my point, however, is that this vital agency is in need of energetic support as well as, perhaps, organizational revision so that it may fulfill its duties properly.

Still another inadequacy is the present Food and Drug Act. The foundation of this act—the principle that the government should concern itself with the safety of drugs and not their efficacy—is nonsensical. Toxicity is inextricably tied in with efficacy and the purpose for which a drug is to be used. A compound which can cure even 10 per cent of patients suffering from a disease otherwise 100 per cent fatal should be allowed on the market even if it carried considerable risk of serious toxicity; a drug alleviating a stuffy nose cannot carry *any* appreciable risk. Since one cannot make an intelligent decision about safety without knowledge of efficacy, it follows that the FDA *has* to deal with efficacy. It further follows, therefore, that the FDA has to evaluate evidence on efficacy. In point of fact, of course, you know it does even now, but in a strange sort of extralegal way. What I should like to see, therefore, is a change in the law bringing the authority of the FDA legally up to date and transforming the act from an Alice-in-Wonderland law to a logical one.

There are more pressing problems, however, deriving from the activities of Congress. One sometimes has the feeling that certain members of Congress see themselves as knights on horseback sallying forth to slay the dragon of disease. I say this in no spirit of mischief, because the committee chairmen dealing with medical research appropriations in the Senate and House command my respect as intelligent, able men.

Nor am I unaware of the fact that informed laymen can discern defects in over-all scientific planning that have eluded the scientists themselves. What I do decry are the following: (1) the notion that our problems can all be solved by huge appropriations and (2) the growing tendency for Congress to attempt detailed direction of scientific research in industry and academic institutions by earmarking funds for specific areas.

The monies available for medical research are no more unlimited than the amounts available for other governmental expenditures. Therefore, there ought to be good reasons for massive expansion in research support other than the pious hope that more and more money automatically means faster progress. In some areas of research (such as cancer chemotherapy) great effort and the talents of all too many workers are currently being wasted because of basic faults in research planning. These faults have been largely undetected because of a lack of critique that I believe is directly attributable to the plethora of funds that has to be spent in this area. The result is a lack of competition for funds, a pressure to "do something" quickly, and the absence of any serious periodic reappraisal, agonizing or otherwise, to justify continued expenditure of funds.

Even more disturbing, in some ways, is the increasing tendency for Congress to dictate types of research by earmarking funds for specific purposes. Congress

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is not capable of detailed direction of research and had best leave that to the scientific advisers who give unstintingly of their time in order that funds may be allocated wisely and justly. Although the government scientists have to follow the mandate of Congress, advisory university scientists do not.

If these latter men feel that they are merely to be rubber stamps, awarding money to undeserving projects, they will no longer serve in an advisory capacity to the government. It is said that thus far Congressional "earmarking" has been limited. True—but it is growing in scope and I suggest that it is easier to stop a trend than to reverse an established practice. In this respect, the stand taken by some of the leaders of the pharmaceutical industry in regard to governmental policies in this area has been noteworthy and admirable.

Now, a few words should be said about problems in clinical research. The task facing clinical pharmacology is tremendous. There are not enough good investigators, there is not enough time, there are too many drugs, and at times it seems as if there are not enough patients. One difficulty, of course, is that industry is too good at coming up with interesting compounds.

What is the answer to these problems? One suggestion is to increase the appeal of clinical pharmacology for talented investigators. To do this requires a variety of approaches, but the basic principles are to raise the prestige value of the field and to make it seem exciting. All too often the title of clinical pharmacologist raises the specter of the uninspired hack turning up dreary data on efficacy and toxicity. Unfortunately, clinical pharmacology has in the past all too often meant *just* this. Nor has the field been helped by those investigators with a reputation for giving a drug house any answer it wants to receive.

What require highlighting are the remarkable tools for research that drugs can be and the fascinating leads to disease processes and mechanisms arising from work-up of a drug. This type of clinical pharmacology, with less emphasis on the inevitable service function of routine drug evaluation, can, I believe, prove appealing to first-rate physicians. Talented investigators must be relieved of heavy, routine loads; they must be free to pick and choose, to pursue leads of interest when they arise. I shall return to one mechanism for achieving this shortly.

The discussion of the positive aspects of gripesmanship is now in order.

1. Many of the problems I have discussed can be resolved by the simple expedient of fighting ignorance. Top men from industry and the universities must communicate more effectively. It helps neither group to meet only with one's own colleagues, pat each other's backs, and shake fists in the direction of the other group.

With men of good will and talent in both areas, it seems impossible to believe that increased respect for one another will not emerge from frank and open meetings. But these meetings must conscientiously avoid platitudes and pleasantries and focus on disagreements and misunderstandings. Perhaps men of ill will should be purposely invited!

2. I suggest that the industry take additional steps to remedy certain of the advertising and promotional errors alluded to earlier. The lack of adequate enforcement of any code of ethics seems to me to preclude effective action. The motion picture industry has seen fit to police its own activities and might be

viewed as a prototype by the pharmaceutical industry. I would much prefer to see reasonable, workable, effective censorship come from within the industry than to see unreasonable censorship imposed on it from without.

3. I would hope that the training of contact men—professional and nonprofessional—in industry would routinely stress the need for avoiding such sore spots as pressures on investigators and the denigration of competitors. I realize that the university world contains just as many undiplomatic and foolish individuals as industry, but unfortunately undiplomatic fools can wreak more general havoc in industry than in the university world.

4. I propose meetings of men from industry, the legal profession, the ministry, and the field of clinical investigation to discuss the problem of human experimentation and the ethical, legal, and financial responsibilities to be met.

5. I recommend that industry expand somewhat its nonproject-oriented support of clinical investigation.

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6. I suggest that industry relieve some of the pressure on the better clinical investigators by increasing its participation in properly controlled experiments. What I propose is this: In a fair number of areas at present, the techniques of controlled trials have been well worked out. It therefore seems most reasonable for drug houses to impose those formats on untrained clinical investigators so that the data collected will be meaningful. In other words, such clinicians will provide the clinical material, and the drug houses will supply the experimental design, coded drugs, randomization schemes, etc. This proposal is not original with me, some drug houses already utilize such a plan. I suggest it to you as a most commendable effort to meet a serious problem and to allow more experienced and imaginative researchers greater leeway for looking at more exciting specific facets of clinical investigation of drugs.

7. I propose that the universities and the pharmaceutical industry join forces in providing reasonable advice to the government. We badly need a lobby both for strengthening the FDA and for preventing unwise participation of the government in drug development. We all have a great deal at stake here, and we must avoid trading short-term gains for long-term disaster.

8. My final suggestion is to increase the amount of industrial public relations work. For example, the public—lay and medical—is barely aware of the many altruistic activities of the drug industry. The public has little appreciation of the various foundations, the fellowships, the support of staff positions, etc., that play so important a role in our scientific life. This is perhaps the finest page, next to the development of new remedies, in the history of the pharmaceutical industry and it is not yet being adequately communicated to the public—and I stress the fact that I refer to more than the medical profession, to the lay public as well.

Before concluding, I should like to refer briefly to one other unsatisfactory aspect of communication—the occasional poor quality of medical journalism. Premature publicity of new agents, unjust accusations, sensational exaggerations—all these have at times been the result of poor newspaper or magazine reporting by journalists eager for a "good story." I realize that newspaper articles

make for better headlines if stories are made black and white instead of gray and if qualifying phrases and reservations are left out, but the result is often a gross distortion of the speaker's remarks and the cause of considerable mischief.

Many responsible scientists try to avoid reporters for this very reason. One eminent elder statesman told me, "The only way to deal satisfactorily with newspapermen is not to let them in the door." If the journalists do not avoid friction and misunderstanding by inadequate reporting, they may find some of the best sources of scientific knowledge shut off to them. People are always giving awards for distinguished scientific reporting. I propose that some noteworthy organization—perhaps the Harvard Lampoon—make an annual Barbed-Wire Bathtub Award for the worst scientific reporting of the year, so as to remind the members of the fourth estate of *their* responsibility.

I am almost through. What has been your reaction? Do you feel that you have been merely listening to an extravagant alarmist or to an uninformed malcontent? If so, I have wasted my time and yours. Or, do you think there are at least some bits of truth in my remarks? If the latter be the case, then you must logically consider whether anything should be done about these points, whether any gains to industry might accrue from changes in policy. I fear that some of my suggestions are not necessarily compatible with financial betterment, since the most admirable companies do not necessarily show the greatest earnings. But there are gains to be won.

I believe that the benefits of avoiding extra-industry censorship, of smoothing relationships between the industry and clinical investigators and practicing physicians and the lay public, and of guiding Congress in the right directions are obvious.

In addition, I believe that certain changes in policy will bring some of our top-notch and influential university clinicians into experimental therapeutics as full-fledged scientific partners with the pharmaceutical industry in the task of developing new remedies. These medical leaders have much to learn, but they also have much to offer; I believe that pharmacologic progress would be considerably more rapid with them as enthusiastic allies rather than as neutrals or hostile enemies.

The final gain is difficult to describe, almost impossible to quantify. I refer to the dynamic effects of working under the conditions most conducive to high morale and increased productivity—the atmosphere engendered by complete pride in one's profession and colleagues, by the knowledge that one need not be on the defensive on any fundamental issue concerning one's professional way of life.

Certainly in universities or hospitals it is often remarkable what the effect of shoddy tactics, of below-par scientific performances by one's colleagues can be. The repetition of such displays can generate feelings of insecurity, instability of personnel, difficulties in attracting superior workers, flagging allegiance, diminished incentive, and decreased productivity. Cannot the same be said of industry? Do the blemishes in the image of industry now presented to the world not prevent industry from achieving the remarkable prestige it is capable of winning?

That most reasonable man, Marcus Aurelius, put it so well some 1,800 years ago: "They kill me, they cut my flesh, they persecute my person with curses. What then? May not thy mind for all this continue pure, prudent, temperate, just? As a fountain of sweet and clear water, though she be cursed by some standerby, yet do her springs nevertheless still run as sweet and clear as before."

There will always be critics standing on the shore, but the knowledge that one's spiritual stream is sweet and clean must help considerably in drowning out their voices.

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ON THE MORTALITY ASCRIBED TO ULCERATIVE COLITIS

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SINCE ulcerative colitis was first described by Sir Samuel Wilks[1] in 1875, it has been regarded as a lethal disease. In 1885 Hale White[2] observed "the treatment unfortunately appears to have very little effect on the disease. . . the prognosis is exceedingly grave." Allchin[3] (1909) was of a similar opinion. While more recent experience justifies a less gloomy view, the reported fatality rate in hospitalized cases remains high. Thus Rice-Oxley and Truelove[4] (1950) in a careful study found that 15 of a series of 69 patients died within the first year. The purpose of this paper is to describe the mortality from ulcerative colitis in the United States and to make some comparisons with the figures available for Canada and England and Wales.

MATERIAL

Tabulations of deaths in the United States ascribed (1) to ulcerative colitis, and (2) to chronic colitis and enteritis not specified as ulcerative, by age, color, sex, and place of residence were obtained[5] for the years 1952 to 1956. In addition, a listing of deaths ascribed to (1) or (2) was provided for 1957[5] and random samples of the microfilm copies of these certificates were examined. Tabulations by age for deaths from ulcerative colitis in Canada were provided by the Dominion Bureau of Statistics for 1952 to 1957.[6] Figures for England and Wales were obtained from the publications of the Registrar-General's office.[7] The total number of deaths on which the analyses have been based are shown in Table III.

Terms which may be assigned to rubric 572.2 of the Sixth Revision of the International Lists of Diseases and Causes of Death[8] are as follows—ulcerative: colitis or enteritis, enterocolitis, and ileocolitis. In addition, colitis with other qualifying terms such as hemorrhagic, infective, or septic, and gastroenteritis may be classified in rubric 572.2 provided the word "ulcerative" is present in the designation. Colitis, enteritis, enterocolitis, gastroenteritis, etc., over the age

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of 2 years neither specified as chronic nor ulcerative are classified in rubric 571.1. Chronic colitis and colitis gravis not specified as ulcerative are classified separately in rubric 572.3 together with the terms as enumerated in the previous sentence if specified as chronic but not ulcerative. Regional enteritis is designated separately as 572.0.

If any clear notion of the mortality ascribed to ulcerative colitis was to be obtained from a study of rubric 572.2, it was important to show (1) that other designations such as ulcerative enteritis and ulcerative gastroenteritis did not account for a material proportion of the deaths thus coded and (2) what proportion of deaths coded to 572.3 had been attributed to the closely related diagnoses of chronic colitis and colitis gravis. Accordingly, random samples of microfilm copies of death certificates ascribed to rubrics 572.2 and 572.3 for 1957 were examined.

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RESULTS

The Samples of Death Certificates.—

Rubric 572.2: In 1957, the primary cause of death of 729 persons within the continental United States was ascribed to rubric 572.2. The actual term used in describing the primary cause of death in a random sample of 104 of these certificates is shown in Table I. The predominant diagnostic term is clearly ulcerative colitis.

TABLE I. TERM USED IN DESIGNATING PRIMARY CAUSE OF DEATH
(Sample of U. S. Deaths, 1957)

Ulcerative colitis	97
Ulcerative enterocolitis	4
Ulcerative enteritis	2
Ulcerative gastritis or gastroenteritis	0
Mesenteric thrombosis (miscode)	1
Total	104

The death certificate also gives the physician an opportunity to describe a sequence of events at death. For example "(a) peritonitis due to (b) perforation of the colon due to (c) ulcerative colitis." In the sample, peritonitis accounted for 23 deaths, intestinal hemorrhage 11, heart failure 7, pneumonia 6, shock 6, pulmonary embolism 4, intestinal obstruction 4, and hepatic failure 3. No immediate cause of death was specified in 28. Other miscellaneous causes made up the remaining 12 deaths.

Table II (*A*) indicates that an autopsy had been performed in approximately one-half of the cases ascribed to this rubric. This is a great deal higher than the over-all figure of 12.5 per cent for all deaths, and of 19.2 per cent for deaths due to gastroenteritis, enteritis, and colitis (rubrics 571 and 572) in the United States in 1949 (the latest year for which figures are available).[9] It is probably related to the fact that almost all (91 per cent) of the 103 deaths occurred in hospitals

or institutions, a figure which is also very much higher than would be expected from the distribution of all deaths in institutions and at home.*

In 1957 some states required that the date and findings of a recent operation should be recorded on the death certificate. In 16 cases death had occurred within 30 days of a colectomy, ileostomy, or exploratory laporotomy, at which corroborative evidence of ulcerative colitis had been found. In 6 of these, no autopsy was subsequently performed, so that confirmation of the clinical diagnosis depended to a large extent on the operative evidence. These cases are included in parentheses in Table II (*A*).

TABLE II. SAMPLE OF U. S. DEATHS FROM ULCERATIVE COLITIS (1957)

A. AUTOPSIES CARRIED OUT (BY AGE)			*B.* LOCATION OF DEATH (BY AGE)		
AGE AT DEATH	AUTOPSY*	NO AUTOPSY*	DEATH AT HOME	DEATH IN HOSPITAL	TOTAL
<5	1	0	0	1	1
5–24	4	7	1	10	11
25–44	9 (+1)†	10	1	18	19
45–64	27 (+5)†	14	0	41	41
65+	10	21	7	24	31
Total	51 (+6)†	52	9	94	103
Miscode	1	0	0	1	1

*Where neither "autopsy" nor "no autopsy" was checked on the certificate, it was assumed not to have been done.

†The meaning of figures in parentheses is explained in the text.

Rubric 572.3: In 1957, 99 deaths were coded to this rubric. A random sample of 26 were examined. One diagnosis of chronic ulcerative colitis had been included in error. Of the remainder, the primary cause of death was ascribed to "chronic colitis" in 11, and chronic diarrhea, chronic enteritis, etc., accounted for 14. Of the "chronic colitis" deaths, 6 occurred in hospitals and in only one had an autopsy been carried out. The general standard of description of the sequence of events and associated conditions at death was lower than in rubric 572.2.

Mortality Rates.—The Sixth Revision of the International List was adopted by the National Office of Vital Statistics in 1949. The total number of deaths from ulcerative colitis, other colitis specified as chronic but not ulcerative, and regional enteritis was first published in 1950, and is available through 1957. The crude annual rates are shown in Fig. 1. and apart from a fall in certification rate for "other chronic colitis and enteritis," there are no definite trends within the period.

*In 1949 approximately one-half of the deaths in the United States occurred at home.[9]

Age: The average age-specific mortality rates from ulcerative colitis for the U. S. population, compared with those for the population of Canada and England and Wales are shown in Table III. After a slight but consistent fall in death rate from infancy to childhood, the rates increase with age in all three countries. The rates for the United States and Canada are very similar. The

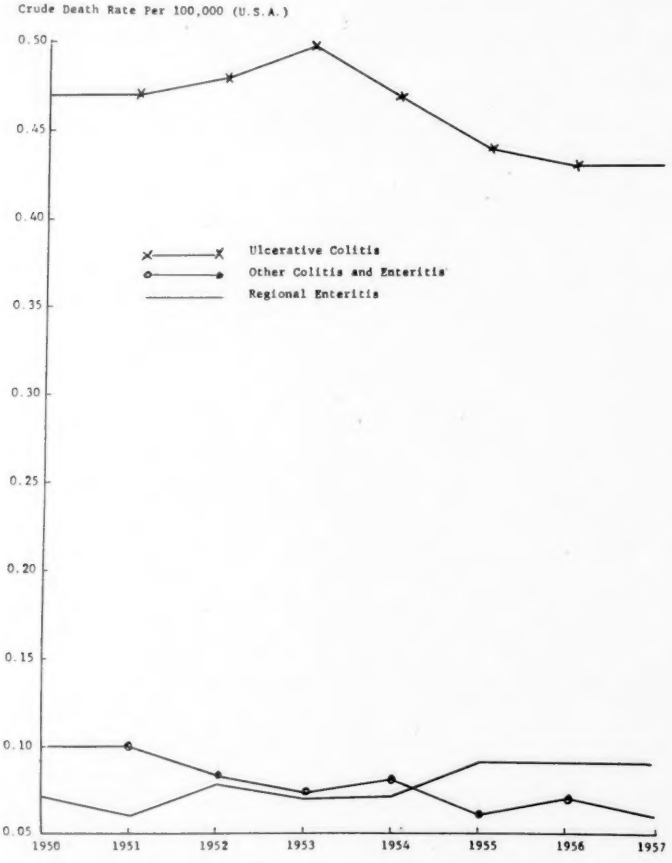

Fig. 1.—Crude deaths rates per 100,000 from ulcerative colitis, regional enteritis, and other chronic colitis and enteritis (1950-1957) U.S.A. (all races).

rates for England and Wales are higher for all groups after the age of 15. If these specific rates are used to calculate age-adjusted rates based on the U. S. population for 1950, the results expressed per 100,000* are as follows: United States 0.47, Canada 0.49, England and Wales 0.85. The age-adjusted death rate from ulcerative colitis in England and Wales is thus almost twice that in the United States and Canada.

*All death rates are estimated per 100,000.

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Race: The age-specific death rates for the white and colored races in the United States are shown in Table III. The death rate in colored persons is lower than in white persons at all ages. If an age adjustment is made the average death rate in colored persons is 0.31 as compared with 0.52 in white people.

TABLE III. DEATHS AND AVERAGE AGE-SPECIFIC DEATH RATES PER 100,000 FROM ULCERATIVE COLITIS

(U.S. 1952-1956; Canada 1952-1957; and England and Wales 1953-1955. Denominators are estimated populations for 1954.)

AGE AT DEATH	UNITED STATES						CANADA		ENGLAND AND WALES	
	WHITE		COLORED		ALL RACES		ALL RACES		ALL RACES	
	5-YEAR DEATHS	AVERAGE DEATH RATE	5-YEAR DEATHS	AVERAGE DEATH RATE	5-YEAR DEATHS	AVERAGE DEATH RATE	6-YEAR DEATHS	AVERAGE DEATH RATE	3-YEAR DEATHS	AVERAGE DEATH RATE
0– 1 1– 4	96	0.1	25	0.02	121	0.1	13	0.1	6	0.1
5–14	58	0.04	3	0.02	61	0.04	6	0.03	8	0.04
15–24	291	0.3	15	0.1	306	0.3	36	0.3	78	0.5
25–34	409	0.4	21	0.2	430	0.4	72	0.5	134	0.7
35–44	474	0.5	33	0.3	507	0.5	56	0.5	221	1.2
45–54	500	0.6	41	0.5	541	0.6	63	0.7	227	1.2
55–64	604	0.9	42	0.7	646	0.9	50	0.7	234	1.6
65–74	576	1.3	29	0.9	605	1.3	73	1.5	229	2.3
75+	485	2.3	22	1.4	507	2.3	60	2.6	159	3.1
	3,495†	0.52*	231	0.31*	3,726†	0.47*	429	0.49*	1,296	0.85*

*Adjusted to the age structure of the U.S. population in 1950.
†Includes 2 deaths in which age was unspecified.

Sex: Age-specific death rates by sex are shown for the United States and England and Wales in Table IV. Figures by sex for Canada were not obtained. In England and Wales the death rate from ulcerative colitis is consistently higher in females at all ages except in childhood for which the figures are very small.* In the United States the relationship is irregular. In white persons the rates are identical in childhood, higher in women between 15 and 44 years, and higher in men from 55 years upward. In colored persons a similar pattern prevails.

*Three male and 3 female deaths under 5 years; 5 male and 3 female deaths 5 to 14 years.

TABLE IV. AVERAGE AGE-SPECIFIC DEATH RATES FROM ULCERATIVE COLITIS BY SEX

(U.S. 1952-1956; England and Wales 1953-1955.
Denominators are estimated populations for 1954.)

AGE AT DEATH	UNITED STATES				ENGLAND AND WALES	
	WHITE MALES	WHITE FEMALES	COLORED MALES	COLORED FEMALES	ALL MALES	ALL FEMALES
< 5	0.1	0.1	0.2	0.3	0.1	0.1
5–14	0.04	0.04	0.01	0.02	0.1	0.03
15–24	0.2	0.3	0.1	0.2	0.4	0.5
25–34	0.3	0.4	0.1	0.2	0.6	0.8
35–44	0.4	0.5	0.2	0.3	0.8	1.6
45–54	0.6	0.6	0.4	0.5	1.0	1.4
55–64	1.0	0.8	0.7	0.7	1.4	1.8
65–74	1.4	1.3	1.0	0.9	1.9	2.7
75+	2.0	2.6	1.2	1.6	2.2	3.6

Place of residence within the United States: Age-adjusted rates have been computed by race for the 4 regions* of the country (Tables V and VI) and by division for all races (Table VII). There is a materially higher death rate from ulcerative colitis in the North East and North Central Regions than in the South, both in white and in colored persons. The interpretation of the figures for the West is complicated by the large migration into that region since the 1950 Census[10] from which the denominators for Tables V and VI have been taken and which will tend to inflate the rates. Estimates of the regional population by color are not available for any subsequent year.

*As defined by the Bureau of the Census.

TABLE V. DEATH RATES FROM ULCERATIVE COLITIS BY REGION FOR WHITE PERSONS CALCULATED BY THE U. S. WHITE REGIONAL POPULATION (1950) ADJUSTED TO THE AGE STRUCTURE OF THE WHOLE U. S. WHITE POPULATION FOR 1950

REGION	NUMBER OF DEATHS OBSERVED	AVERAGE AGE-ADJUSTED DEATH RATE
North East	1,218	0.62
North Central	1,093	0.50
South	630	0.38
West	554	0.59
U. S. A.	3,495	0.52

TABLE VI. DEATH RATES FROM ULCERATIVE COLITIS BY REGION FOR COLORED PERSONS CALCULATED BY THE COLORED REGIONAL POPULATION (1950) ADJUSTED TO THE AGE STRUCTURE OF THE WHOLE U. S. COLORED POPULATION FOR 1950

REGION	NUMBER OF DEATHS OBSERVED	AVERAGE AGE-ADJUSTED DEATH RATES
North East and Central	86	0.39
South	119	0.23
U. S. A.*	231	0.31

*Including 26 colored deaths from ulcerative colitis in the West.

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An attempt was also made to determine the relationship of residence in urban and rural places to the death rate from ulcerative colitis. Comparisons were made between the aggregate populations of places with a population of 10,000 or more in 1950 and the remainder. The crude average death rate in the urban aggregate was 0.61; that in the rural aggregate 0.38. This difference is in part due to the fact that the urban population is slightly older than the rural.

Other chronic colitis and enteritis: In the United States, colitis and enteritis specified as chronic but not ulcerative was certified as the primary cause of death in an average of 125 deaths per annum in the years 1952 to 1956, approximately

TABLE VII. AVERAGE DEATH RATES (AGE ADJUSTED TO U. S. POPULATION 1940) FOR ULCERATIVE COLITIS, OTHER CHRONIC COLITIS, AND ALL FORMS OF DYSENTERY BY DIVISION, ALL RACES

REGION	ULCERATIVE COLITIS— 1952-1956 AVERAGE AGE-ADJUSTED DEATH RATES	OTHER CHRONIC COLITIS AND ENTERITIS— 1952-1956 AVERAGE AGE-ADJUSTED DEATH RATES	ULCERATIVE COLITIS AND CHRONIC COLITIS AND ENTERITIS	DYSENTERY— 1949-1951 AVERAGE AGE-ADJUSTED DEATH RATES
New England	0.56	0.07	0.63	0.1
Middle Atlantic	0.60	0.06	0.66	0.1
East North Central	0.50	0.07	0.57	0.2
West North Central	0.42	0.07	0.49	0.2
South Atlantic	0.36	0.06	0.42	0.6
East South Central	0.32	0.13	0.45	1.3
West South Central	0.28	0.13	0.41	2.5
Mountain	0.44	0.11	0.55	1.0
Pacific	0.60	0.06	0.66	0.2

one-sixth as frequently as ulcerative colitis. As can be seen from Fig. 2, such certifications are almost unknown between the ages of 14 and 44. Unlike certifications from ulcerative colitis they are more frequent in the South than the North (Table V), and are equally distributed between town and country, as defined above.

The pattern of mortality from dysentery in the United States: In view of the opinion held by some that ulcerative colitis is related to dysentery, a comparison of their patterns of distribution is relevant. Table VII gives the average death rates (age-adjusted) from all forms of dysentery by division for 1949 to 1951,[11]

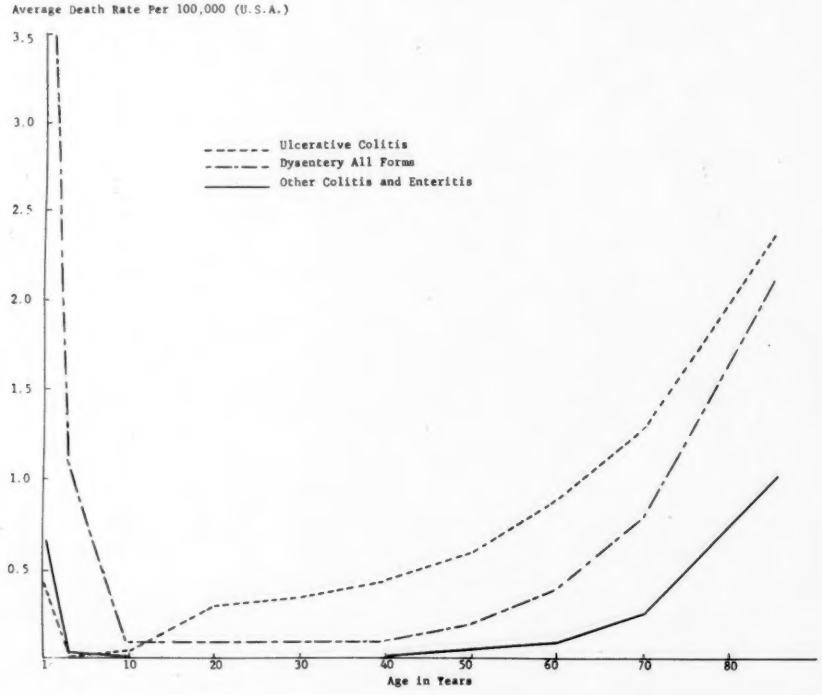

Fig. 2.—Average age-specific death rates per 100,000 for ulcerative colitis (1952-1956), other chronic colitis and enteritis (1952-1956), and dysentery, all forms (1949-1951) U.S.A. (all races).

compared with the average death rates (age-adjusted) from ulcerative colitis for the period 1952 to 1956. The table shows a striking contrast in the distribution of the two disorders. Deaths from dysentery are 25 times more frequent in the South West than in the North East while the mortality from ulcerative colitis in the South West is about one-half that in the North East.

DISCUSSION

Ulcerative colitis is generally regarded as a convenient term for inflammatory reactions of the large bowel which cannot be attributed to infection with the

Endamoeba histolytica or bacillary dysentery, nor to other specific causes such as uremia, antibiotics or tuberculosis. Although it has certain fairly characteristic clinical and pathologic features, it is doubtful whether ulcerative colitis can be defined entirely in positive terms at present. In assessing the mortality pattern, therefore, it should be noted that the term is at best an indefinite one which may eventually be found to contain more than one disease entity.

A study of a sample of U. S. deaths coded to rubric 572.2 showed that in 94 of 104 cases the certifying physician attributed death to ulcerative colitis. While in 2 of these 94 cases information on the rest of the certificate suggested that the underlying cause of the colonic ulceration might have been uremia, in the remaining 92 (88.5 per cent) there was no evidence to suggest that the term "ulcerative colitis" had not been used in the generally accepted sense outlined above. Although complete confidence in the rubric could only be assured by tracing and studying individual case records, which was beyond the scope of this investigation, further assurance about the standard of diagnosis was obtained from the almost invariable occurrence of death in hospitals and from the very high autopsy rate.

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A more difficult problem is to determine what deaths due to ulcerative colitis were classified elsewhere. The examination of a sample of deaths in rubric 572.3 showed that about one-half were attributed to "chronic colitis." If the sample is representative, an average of only about 60 deaths (i.e., less than 10 per cent of the average number of deaths ascribed to ulcerative colitis) will have been designated in this way each year during the period under study. The standard of description of the deaths in this rubric was found to be poor. Colitis, unspecified as either chronic or ulcerative, is contained with a large number of cases of gastroenteritis and enteritis. This rubric was not examined.

It is important to note that, at the present time, deaths attributed to carcinoma of the colon or rectum due to ulcerative colitis are coded to the appropriate carcinoma in all three countries studied in this paper.

The increasing death rate with age demonstrated in this material is on fairly firm ground. It is consistent in three countries. Even if age-specific rates were constructed only from those deaths which were believed to have been corroborated by autopsy or by the findings at a recent operation (Table II, *A*), the rates would show an increase up to the age of 65 with a slight decrease thereafter.

Nevertheless, as in other diseases, it is likely that diagnosis is less accurate in old age. Thus in persons whose deaths were attributed to ulcerative colitis over the age of 65, death occurred more frequently at home and autopsy was less frequent than in younger persons (Table II). Although it is true that ulcerative colitis is generally regarded as a disorder of youth and early middle age,[12,13] various authors have drawn attention to its occurrence in later life.[14,15] In hospital series, in which the numbers of old people with ulcerative colitis are small,[4,16-19] due allowance should be made for the relatively smaller numbers of old persons in the populations from which these patients are derived.

As far as deaths in infancy are concerned, it is hard to escape the conclusion that some deaths attributed to ulcerative colitis were in fact due to specific enteric infections. Thus although ulcerative colitis in childhood has been fre-

quently described, published instances in the first year of life are extremely rare. In 95 cases in children reported by Jackman and his associates,[20] the onset was invariably after the first birthday. This was also true of 139 children described by Kennedy and Bargen.[21] In 1947 Cabot[22] described a fatal case in an infant aged 3 months and referred to two others. Coll and Stevenson[23] have recently described one other case commencing in the second week of life.

Against this background it was surprising to learn that in the United States between 1952 and 1956, 99 deaths within the first year of life were attributed to ulcerative colitis. In 1957 when more details were available 13 such deaths were reported, 3 of which occurred within 30 days of birth. These early deaths and the effect which they have on the age-specific death curve (Fig. 2) should be accepted with reserve.

The death rates from ulcerative colitis are very similar for the United States and Canada. The higher rate in England and Wales is striking. If the sexes are considered separately (Table IV) it can be seen that the death rates in England and Wales are higher at all ages but that the excess in female deaths in England and Wales is particularly apparent. This table discloses a further feature, namely, that while there is no consistent sex difference in death rates in the United States, there are higher rates in women than in men in England and Wales at all ages.

Unless they are due to different certification and coding techniques which seems unlikely, particularly as far as the sex differences are concerned, these differences must be due either to an increased prevalence of ulcerative colitis in England and Wales, particularly in women, or to a more fatal form of the disorder. Unfortunately, comparable morbidity studies are not available. However, as far as sex differences are concerned, some comparisons may be made in terms of the composition of recent hospital series of cases in the two countries. Thus in England and Wales, Rice-Oxley and Truelove[4] and Cullinan and MacDougall[19] found that females predominated. In the two series 62 per cent of an aggregate of 475 cases were women. If the series of Sloan,[16] Flood,[17] and Hightower[18] and their co-workers from the United States are combined, 46 per cent of an aggregate of 2,368 cases were women. Although hospital series should be interpreted with caution in view of the unknown factors of selection which may be operating, these figures support the view that ulcerative colitis is more prevalent in women in the United Kingdom but not in the United States.

Within the United States the death rate from ulcerative colitis for colored persons is approximately three-fifths that for white persons. When differences in age structure of the two populations are allowed for, there is also a relatively lower death rate of the same order of magnitude for white people in the South as compared with the North and West, and for colored persons in the South as compared with the North. These figures may reflect a real difference in the pattern of the disease as suggested by Bacon[12] and Texter,[24] but they are difficult to interpret because it is known that the standard of death certification is lower in some Southern States than in the North, and in colored persons than in white persons. Thus in 1950 the crude death rate from symptoms and ill-defined conditions other than senility (rubrics 780-793, 795) for the Middle Atlantic States was 5.1 for white persons and 14.0 for colored persons; for the East South Cen-

tral States it was 23.2 for white people and 127.7 for colored persons.[9] A further point against a "real" North-South difference within the North American continent is the essential similarity of the Canadian and American death rates.

The apparent excess of deaths in cities with a population of at least 10,000 may also be due to better standards of diagnosis and certification in urban areas than in the country.

Accurate morbidity data for ulcerative colitis would clarify the significance of these regional and racial differences.

Table VII shows the contrast between the geographic patterns of mortality from dysentery and ulcerative colitis. The morbidity pattern for dysentery is probably similar.[25] The lowest death rates for ulcerative colitis are found in the two divisions (East South Central and West South Central) with the highest death rates for dysentery. It is possible that some deaths due to ulcerative colitis are ascribed to dysentery in these regions. However, when it is seen that the reverse also holds and that divisions with the highest death rates from ulcerative colitis also have the lowest death rates from dysentery, it becomes reasonable to suppose that the diseases are generally unrelated to one another. According to Melrose,[26] a similar inverse relationship exists between the mortality from dysentery and ulcerative colitis in Scotland as compared with England and Wales. This does not rule out the possibility of an etiological association in rare instances.

The mortality from regional enteritis is described elsewhere.[27]

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CONCLUSIONS

1. The death rate attributed to ulcerative colitis in England and Wales is almost twice that found in the white population of the United States and Canada.
2. The death rate increases with age in all three countries.
3. In England and Wales the death rate from ulcerative colitis is higher in women at all ages than in men. In the United States there is no consistent sex difference, although the female death rate is higher in young adults.
4. Within the United States deaths from ulcerative colitis are reported less frequently in colored persons (other races) than in white persons, in the South than in the North and West, and in the country than in the towns.
5. There is an inverse relationship between the mortality pattern of ulcerative colitis and the pattern of deaths from all forms of dysentery.
6. Within the short period for which comparable figures are available there has been no definite change in the death rate from ulcerative colitis in the United States.
7. In a sample of death certificates, peritonitis and intestinal hemorrhage were the most prominent immediate causes of death.

This study was commenced while I was Radcliffe Travelling Fellow of Oxford University in the United States. I wish to acknowledge the critical advice of Drs. Martin M. Cummings, Clifford A. Bachrach, and Abraham Lilienfeld, and the help of Miss Marlene Schwartz in preparing the manuscript.

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ON THE MORTALITY ASCRIBED TO REGIONAL ENTERITIS

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ALTHOUGH nonspecific granulomas of the small bowel have been recognized for many years, it was not until 1932 that "regional ileitis" received its first definitive clinical and pathologic description.[1] The occurrence of the lesion in the upper as well as the lower part of the small intestine soon led to the suggestion of a modified name—"regional enteritis"—by Brown, Bargen, and Weber.[2] In this paper these two terms will be regarded as synonymous with "Crohn's disease." An attempt will be made to delineate the pattern of mortality ascribed to this condition in the United States, and to make some comparisons with Canada and England and Wales. The mortality pattern of ulcerative colitis has already been described.[3]

MATERIAL

In the Sixth Revision of the International Statistical Classification,[4] regional enteritis was placed in rubric 572.0. Terms which may be coded thus are: Crohn's disease; ileitis, regional; and enteritis, regional. The specificity of the rubric is therefore admirable. Enteritis if specified as ulcerative is coded in 572.2, as chronic but not ulcerative in 572.3, and unspecified in 571.1.

Tabulations of deaths in the United States for which regional enteritis was certified as the primary cause were obtained for the years 1950 and 1952 to 1956.[5] In addition, a random sample of microfilm copies of the death certificates for 1957 was examined.[5] A tabulation of deaths by age was obtained from the Dominion Bureau of Statistics of Canada for the years 1952 to 1957,[6] and published material for 1952 to 1956 for England and Wales was also examined.[7] The total number of deaths on which the analyses have been based is shown in Table II.

RESULTS

The Sample of Death Certificates.—In 1957 the primary cause of death of 151 persons in the United States was ascribed to regional enteritis. A random sample of 53 microfilm copies of these death certificates was examined. In 51

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cases the words used to describe the cause of death were regional enteritis, regional ileitis, or terminal ileitis*; one case of regional colitis had been coded thus, and one case of "idiopathic chronic diarrhea" had been miscoded to this rubric.

Table I shows the distribution of the deaths in hospital and at home, and the frequency of autopsies by age. The figures in parentheses in Table I (*A*) indicate instances in which no autopsy had been performed, but corroboration of the diagnosis had been obtained at an operation within 30 days of death. Either an autopsy or an operation had been performed in 33 (63 per cent). As in ulcerative colitis[3] almost all the deaths occurred in hospital, and the autopsy rate was high.

TABLE I. SAMPLES OF U. S. DEATHS FROM REGIONAL ENTERITIS (1957)

A. AUTOPSIES CARRIED OUT BY AGE			*B*. LOCATION OF DEATH BY AGE		
AGE AT DEATH	AUTOPSY*	NO AUTOPSY*	DEATH AT HOME	DEATH IN HOSPITAL	TOTAL
< 5	0	0	0	0	0
5–24	4 (+2)†	2	0	6	6
25–44	4 (+1)†	6	2	8	10
45–64	9 (+2)†	12	2	19	21
65 +	7 (+4)†	8	1	14	15
Total	24 (+9)†	28	5	47	52
Miscode	0	1	1	0	1

*Where neigher "autopsy" nor "no autopsy" was checked on the certificate, it was assumed not to have been done.

†For meaning of figures in parentheses see text.

The immediate cause of death was also studied. Death was ascribed to peritonitis following perforation of the bowel in 13; intestinal obstruction in 10; intestinal hemorrhage in 4; pulmonary embolism in 4; and cardiac failure in 4. Of the remainder, miscellaneous causes were described in 7 and the immediate cause of death was unspecified in 10. As in ulcerative colitis[3] the general standard of description of these deaths was high.

The closely related rubrics 572.2 and 572.3 were also studied.[3] Of 104 death certificates classified in 572.2, 2 gave "ulcerative enteritis" as the cause of death; in 572.3, 4 of 26 deaths were due to "chronic enteritis." The meaning of these terms is unknown but it is reassurring that they are rarely used. If the samples are representative, about 30 deaths are ascribed to these causes annually in the United States. The composition of rubric 571.1 in which "enteritis, unspecified" is included among a large number of other terms is unknown.

*This ambiguous term was used in 4 cases.

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Death Rates.—In the United States mortality figures for regional enteritis have been available since the Sixth Revision of the International Statistical Classification[4] was put into effect. There has been no striking change in death rate within the years 1950 to 1957 although the rates reported in 1955, 1956, and 1957 have been slightly higher than those reported previously.[3]

TABLE II. DEATHS AND AVERAGE AGE-SPECIFIC DEATH RATES PER 100,000 FROM REGIONAL ENTERITIS

(U.S. 1950, 1952-1956; Canada 1952-1957; England and Wales 1952-1956. Denominators are estimated populations for 1954.)

AGE AT DEATH	UNITED STATES						CANADA		ENGLAND AND WALES	
	WHITE		COLORED		ALL RACES		ALL RACES		ALL RACES	
	6-YEAR DEATHS	AVERAGE DEATH RATE	6-YEAR DEATHS	AVERAGE DEATH RATE	6-YEAR DEATHS	AVERAGE DEATH RATE	6-YEAR DEATHS	AVERAGE DEATH RATE	5-YEAR DEATHS	AVERAGE DEATH RATE
<5	16	0.02	3	0.02	19	0.02	0	0.0	0	0.0
5–14	6	0.01	1	0.01	7	0.01	0	0.03	0	0.0
15–24	39	0.03	1		40	0.03	8		12	0.03
25–34	90	0.07	7	0.07	97	0.07	11	0.07	40	0.1
35–44	107	0.09	15		122	0.09	7		58	0.2
45–54	132	0.13	14	0.11	146	0.13	13	0.2	49	0.2
55–64	136	0.17	6		142	0.17	12		50	0.2
65–74	101	0.2	9	0.2	110	0.2	9	0.3	49	0.3
75+	69	0.27	2		71	0.26	11		24	0.3
	697*		58		755*		71		282	

*Age unknown in one case.

Age: The average age-specific mortality rates from regional enteritis for the U. S. population are compared with those for Canada and England and Wales in Table II. In adult life the rates for England and Wales are slightly but consistently higher than those for Canada and the United States. Adjusted to the age structure of the U. S. population in 1950, the average rates are as follows: United States 0.08, Canada 0.09, England and Wales 0.11.* The curves are compared with those for ulcerative colitis in Fig. 1. The death rates from regional enteritis rise in a linear fashion with age, but much less steeply than ulcerative colitis.

*All death rates are calculated per 100,000.

Race: Within the United States the average age-adjusted death rate in white persons is 0.08 and in colored persons is 0.06. This difference is slight. It is almost entirely due to a deficiency of deaths coded to this cause in Southern Negroes (Table V).

Sex: In the United States during the years 1950, and 1952 to 1956, 755 deaths from regional enteritis were reported: 431 in males and 324 in females. For England and Wales (1952 to 1956), the figures are 137 men and 145 women.

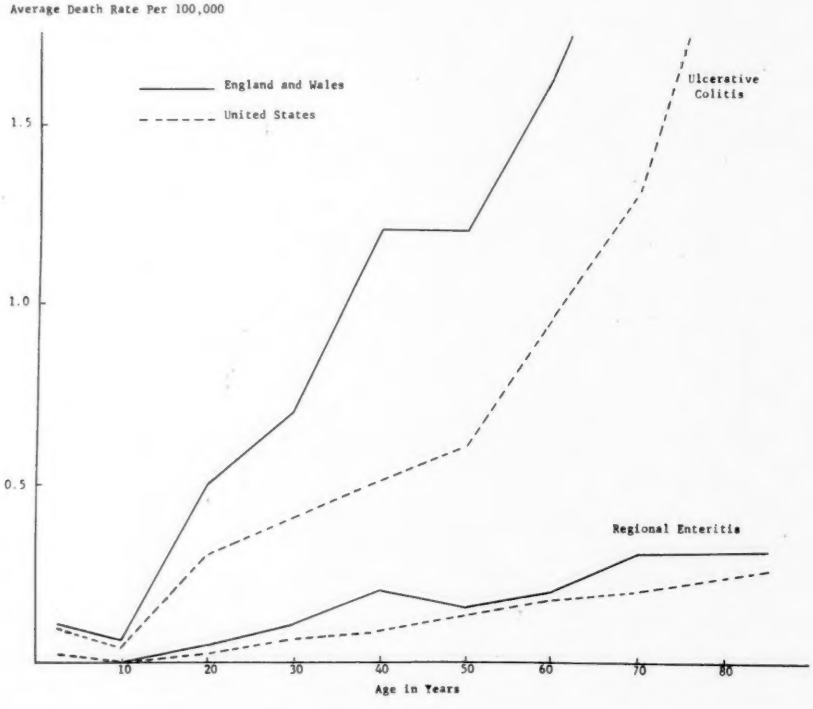

Fig. 1.—Average age-specific death rates per 100,000 for ulcerative colitis and regional enteritis U.S.A. (all races) and England and Wales.

Sex-specific death rates by age are shown in Table III. In the United States the death rate from regional enteritis is consistently higher in men of 25 years of age and upward than in women. For England and Wales the relationship between the sex-specific death rates is irregular at the various ages and the over-all rates are similar.

Place of residence within the United States: Race-specific average death rates are shown by region* in Tables IV and V. The rates for white persons are age adjusted. Since the number of deaths in colored races is too small for age adjustment, the median age is also given in Table V. In white people deaths are reported

*As defined by the Bureau of the Census.

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with three-fifths the frequency in the South that they are in the North East. The death rates for the North Central and Western Regions are similar to those of the North East. In colored persons the death rate in the North East and North Central regions is comparable to that for white people, and a relative deficiency in deaths reported from the South is also noted.

TABLE III. AVERAGE AGE-SPECIFIC DEATH RATES BY SEX
(U.S. 1950, 1952-1956; England and Wales 1952-1956.
Denominators are estimated populations for 1954.)

AGE AT DEATH	ALL RACES			
	UNITED STATES AVERAGE DEATH RATES		ENGLAND AND WALES AVERAGE DEATH RATES	
	MALES	FEMALES	MALES	FEMALES
0– 4	0.02	0.02	0.0	0.0
5–14	0.01	0.01	0.0	0.0
15–24	0.03	0.03	0.06	0.02
25–34	0.07	0.06	0.09	0.16
35–44	0.10	0.08	0.24	0.13
45–54	0.15	0.11	0.18	0.14
55–64	0.22	0.12	0.23	0.20
65–74	0.23	0.17	0.26	0.32
75+	0.30	0.22	0.22	0.31

TABLE IV. DEATH RATES BY REGION FOR WHITE PERSONS CALCULATED BY THE U. S. WHITE REGIONAL POPULATION ADJUSTED TO THE AGE STRUCTURE OF THE U. S. POPULATION FOR 1950

REGION	NUMBER OF DEATHS IN WHITES OBSERVED (6 YEARS)	AVERAGE AGE-ADJUSTED DEATH RATES IN WHITES
North East	245	0.10
North Central	228	0.09
South	119	0.06
West	105	0.09
U. S. A.	697	0.09

To obtain some notion of the urban/rural distribution of mortality, the rate for residents of urban places with a population of 10,000 or more in 1950 (aggregate population 73,916,000) was compared with the rate for residents of the rest of the population (aggregate population 76,781,000). For the urban aggregate, the crude average death rate was 0.10; for the remainder 0.07. Part of this difference is due to the fact that townspeople in the United States are slightly older than country people.[8]

TABLE V. CRUDE AVERAGE DEATH RATES FOR COLORED PERSONS BY REGION
(Denominator U. S. Colored Population 1950)

REGION	NUMBER OF DEATHS COLORED OBSERVED (6 YEARS)	AVERAGE CRUDE DEATH RATE COLORED	MEDIAN AGE IN YEARS
North East and Central	25	0.09	29.2
South	25	0.04	24.2
West	8	0.14	27.6
U. S. A.	58	0.06	26.1

DISCUSSION

A random sample of death certificates showed that, like ulcerative colitis,[3] a very high autopsy rate prevails in deaths ascribed to regional enteritis. This is partly related to the fact that almost all the deaths occurred in hospitals but may also reflect medical interest in an unusual disorder. The fact that perforation and peritonitis was the immediate cause of death in 13 of 52 cases is surprising in view of the opinion that the tendency of the lesion to proliferate, sclerose, and form adhesions protects against this complication.[9,10]

Regional enteritis is certified as the cause of death with about one-sixth the frequency of ulcerative colitis in the United States and Canada.[3] In England and Wales the ratio is about 1 to 7.5.[3]

The differences in sex patterns are interesting. The higher death rates in adult American males at all ages suggest either an increased prevalence or a more fatal type of disease in this group. Some support for the former view is given in the large series of Crohn (1949)[9] and Van Patter and his colleagues (1954)[10] in both of which slightly over one-half the patients were men.

In spite of the fact that the gradient of the curve is much less steep than that for ulcerative colitis (Fig. 1), the age-specific death rates do not support Van Patter's[10] view that regional enteritis is a disease predominantly affecting young people.

The regional and racial pattern of deaths due to regional enteritis within the United States is very similar to that from ulcerative colitis; the rates are lower in colored persons than in white, in the South than in the North and West, and in the country than in the town. Although differences of this magnitude and in these directions are difficult to interpret,[3] the fact that the death rate among colored persons in the North East and Central Regions is similar to that among white people in these regions is of interest, particularly in view of Boyce's[11] and Daffner and Brown's[12] opinion that the condition is rare in Negroes.

The mortality pattern of regional enteritis is very different from the distribution of sarcoidosis with its striking prevalence in the Southern States and its racial predilection for Negroes.[13,14] This is a further point against any biologic relationship between these conditions.[15]

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CONCLUSIONS

1. The average age-adjusted death rates ascribed to regional enteritis in recent years have been as follows: United States 0.08, Canada 0.09, England and Wales 0.11 per 100,000. The death rates from ulcerative colitis in the same period have been five to seven times as great in the various countries.

2. In the United States the death rate in males is slightly higher in all adult age groups than in females. In England and Wales there is no material difference between the death rates in the two sexes.

3. The death rate from regional enteritis increases with age in all three countries but much less steeply than does the death rate from ulcerative colitis.

4. Within the United States the death rate ascribed to regional enteritis is lower in the South than in the North and West in all races, but the differences are slight and difficult to interpret.

5. In a sample of death certificates, peritonitis due to perforation and intestinal obstruction were the most prominent immediate causes of death.

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This study was commenced while I was Radcliffe Travelling Fellow of Oxford University in the United States. I wish to acknowledge the critical advice of Drs. Martin M. Cummings, Clifford A. Bachrach, and Abraham Lilienfeld, and the help of Miss Marlene Schwartz in preparing the manuscript.

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Review

HUMAN TOXOPLASMOSIS

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ALTHOUGH it has been only 20 years since Toxoplasma was demonstrated to cause human illness[1] and about a decade since precise laboratory tests were devised,[2-4] interest in it has progressed from that of laboratory curiosity to full-fledged clinical importance in both human and veterinary medicine. As good an index as any of the maturity of toxoplasmosis as a disease entity is the number of reviews that have been published in recent years.[5-8] This summary will not attempt to repeat details which are covered adequately in the other reports but, rather, to concentrate on those aspects of toxoplasmosis that are of particular interest to physicians concerned with adult medicine.

THE PARASITE

Toxoplasma gondii is an obligate, intracellular parasite which can invade and multiply in all cells of all tissues of animals and birds. Erythrocytes have been assumed to be an exception to this generalization, but a recent report demonstrates that they may be invaded provided they are nucleated (e.g., in chick embryo).[9] The parasite usually measures 2 to 4 by 4 to 7 microns and in fresh preparations has the appearance of a crescent with one end somewhat rounded and the other pointed, but may appear ovoid when fixed in tissues. *T. gondii* can best be stained with Giemsa's or Wright's stain, although it can be identified in hematoxylin and eosin preparations. The cytoplasm is dyed pale blue and the nucleus red with Giemsa's and Wright's stains. Multiplication is by binary fission.

Probably because of their intracellular location, live parasites may be obtained from the tissues of humans and other animals months and years after presumed recovery from active infection. Aggregations of parasites which have the appearance of cysts may be demonstrated after careful and prolonged histologic examination of hematoxylin and eosin or para-aminosalicylic acid stained

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sections. These have been called "pseudocysts" on the assumption that the surrounding membrane was a product of the host, rather than of the parasite. It now appears that the limiting membrane is a product of the parasite and the structures are true cysts.[10-12] Organisms contained in cysts remain viable indefinitely, if not for the lifetime of the host. It is quite likely, therefore, that once an animal becomes infected he remains infected for the duration of his life.

Toxoplasma has been isolated from many varieties of wild and domesticated animals, in addition to man. Among these are cats, dogs, sheep, cattle, rats, bandicoots, horses, swine, foxes, mink, squirrels, guinea pigs, rabbits, mice, chinchillas, primates, etc. Among the birds, parasites have been found in pigeons, chickens, ducks, and penguins. Young animals tend to have more severe manifestations accompanied by a higher fatality rate than the older, more mature ones.

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DEMONSTRATION OF THE INFECTION

This is best proved, directly, by demonstrating the parasite in the case under suspicion or, indirectly, by serologic means.

Since the parasite requires living tissues for multiplication, isolation is best performed by inoculating laboratory-reared albino mice. These are almost always free of natural infection and uniformly susceptible but individual parasite strains may require different numbers of passages in which to adapt themselves to produce consistently lethal infections in the mice. The method employed for this purpose depends somewhat upon the source of the material under study. If the patient has encephalitis, organisms may be sought in the spinal fluid by either of two methods.

By one technique, the sediment of the spun spinal fluid may be smeared and stained by Giemsa's or Wright's method; parasites may be seen quite readily in in such preparations. Isolation from the spinal fluid should be attempted by resuspending the sediment in a small volume of supernate and dividing this between 3 to 6 mice by intraperitoneal inoculation. Blind passages should be performed at 14-day intervals by suspending pools of spleen and brain and making passages into fresh mice. At least three blind passages should be attempted before the trial is discontinued. Fresh, not frozen, material should be used for passage.

An alternative method is to leave the animals alone for 3 weeks, after which time they should be bled and the sera of several pooled and examined for dye-test antibody. If this is present the mice are sacrificed, their tissues pooled, and passages made. Of course, the tissues of any animal that becomes ill or dies during the period of observation should be transferred to fresh animals. Should ascites be noted, abdominal paracentesis will produce a drop of fluid that may reveal parasites in profusion upon examination of a wet film.

When attempting isolation from host tissues, either of two methods may be used. A piece of tissue may be minced with scissors, ground without an abrasive (sand), and suspended to about 10 to 20 per cent concentration either in saline containing 0.5 per cent gelatin or in 10 per cent inactivated rabbit serum. After

permitting the gross particles to settle during brief cold storage, the suspension is inoculated intraperitoneally into laboratory mice.

More recently, Jacobs and Melton[13] have devised a method which appears to be superior for demonstrating organisms contained in cysts. The procedure is based on the assumption that parasites present in cysts are more resistant to a pepsin-hydrochloric acid solution than are proliferating Toxoplasma. As much as 125 Gm. of tissue is ground and suspended in the following solution: 1.3 Gm. pepsin (1:10,000), 2.5 Gm. NaCl, 3.5 ml. HCl (conc.), and distilled H_2O to make 500 ml. total volume. Permit digestion with constant agitation for 2 hours at 37° C. Filter through cheese cloth, centrifuge for 10 minutes at 2,000 r.p.m., discard the supernate, and resuspend the sediment in saline. After recentrifugation, resuspend the sediment in an amount of saline sufficient to make a total volume of 20 ml. A group of mice are then inoculated intraperitoneally with 1 ml. aliquots. The injections may be repeated the following day with the remaining material that has been refrigerated overnight. Jacobs has applied this system with particular success in studies of the prevalence of Toxoplasma in the diaphragms of rats, swine, and cattle. He believes that animal infections are more readily acquired, orally, from chronic rather than acute infections.[12] This is based on the assumption that chronically infected animals possess large numbers of cysts and that the organisms so contained are more resistant to digestive trauma than the proliferative forms which predominate in acute infections. They found, for example, that the digestion of brains of chronically infected rats with pepsin-hydrochloric acid solution produced noninfection after 4 but not 3 hours. Encysted parasites apparently lost viability rapidly at temperatures of 50° C. or more.

In human cases the digestion method probably would have its greatest use when the isolation of parasites is attempted from muscle or lymph node tissue removed by biopsy or from other tissues obtained during postmortem examination or by surgical excision (e.g., from the eye).

Currently there are four immunologic methods which may be used to detect either active or previous infections with Toxoplasma. Three of these employ serum: the dye,[2] hemagglutination,[14] and complement-fixation[15] tests. The fourth is the skin[16,17] test. Each has been discussed quite completely by various writers and will not be considered in detail at this time. Only their principles will be reviewed briefly.

Dye Test.—Fresh parasites obtained from mouse peritoneal exudate are suspended in fresh, nonantibody-containing, normal human serum. Equal amounts of this are then mixed with varying fourfold dilutions of the serum (inactivated for 30 minutes at 56° C.) the antibody content of which is being measured. Following incubation for 1 hour at 37° C., a small amount of alkaline methylene blue (pH 11.0) is added and the proportion of stained and unstained extracellular parasites is determined by examining a wet film. The titer of the serum is the reciprocal of the original serum dilution in which 50 per cent of the organisms are unstained. Basically, the test measures the Toxoplasma-killing ability of an antibody-containing serum. The antibody itself does not accomplish this except in the presence of a heat-labile serum system, which has

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been called "activator," similar to, if not identical with, the properdin system.[18] Normal human (without antibody) and mouse sera do not kill Toxoplasma, that is, they do not produce unstained parasites. The fresh, active sera of all other animals and birds and almost all fresh-water fish[19] that have been studied to date have been found to kill parasites in the absence of specific antibody.

The function of the dye has often been misinterpreted; it was included by the original authors only as a convenience for counting parasites. They demonstrated that antibody and activator not only killed the parasites (on the basis of mouse inoculation) but also induced visual and physical changes in the cell wall. Upon examination of such organisms in a wet film, it is found that the distinctness of the surrounding membranes of the antibody-affected parasites has been lost; if they are permitted to dry on the slide they disintegrate. In the absence of antibody, the membranes remain sharp and distinct and do not rupture on drying. It was noted, also, that intracellular parasites in the peritoneal exudate were unaffected by antibody and activator, affording a visual demonstration of the inability of the antibody to penetrate the macrophage wall.

The dye test is very sensitive and specific for detecting Toxoplasma antibodies. Questioning of its specificity has failed to receive experimental support. Dye-test antibodies appear soon after the onset of clinical symptoms, rise to a peak in a few weeks, and persist in slowly diminishing titer for many years, if not for life. The chief drawback of the test is that it requires living organisms, which not only induces certain biologic problems but also presents something of a hazard to laboratory personnel. It would be wise, perhaps, to select people who already have antibodies and who are not pregnant to perform the test and otherwise work with live Toxoplasma.

Hemagglutination Test.—This procedure recently has been described by Jacobs and Lunde.[14] It appears to measure an antibody similar to that detected in the dye test, but has one potential advantage in that it does not require the presence of living organisms. Experience with this procedure is still limited, but the test is likely to assume an important place in Toxoplasma serology.

The antigen is made by lysing washed parasites with distilled water. It keeps fairly well in the frozen or lyophilized states, but deteriorates in the liquid form, especially at higher temperatures. The erythrocytes that are used as vehicles may be either sheep or type O human cells, pretreated with tannic acid (1:80,000), and then sensitized with the antigen. The sera to be tested should be absorbed first with sheep cells if such erythrocytes are to be used for hemagglutination.

The antibodies measured in this test appear somewhat less rapidly than dye-test antibodies but they seem to persist for about as long.

Complement-Fixation Test.—Any standard complement-fixation system can be used with antigen prepared from either infected chorio-allantoic membranes (chick) or mouse peritoneal exudate. In either case, the source material is frozen and thawed several times and then clarified by centrifugation. The supernate contains the antigen which is stable. Egg antigen is preferable because precise control material may be made from uninoculated eggs. Mouse peritoneal exudate antigen generally is the more potent and usually can be diluted further, even though it may be anticomplementary at the more concentrated levels.

Complement-fixing antibodies are produced more slowly than either dye or hemagglutination antibodies and disappear more rapidly. Thus, either very early or months after onset of an infection, the former may be negative and the latter two test markedly positive.

Skin Test.—The antigen used here is the same as for the complement-fixation test; the reaction is of the delayed tuberculin type. Skin sensitivity is acquired slowly, requiring about a year for positive reactions to develop. It probably persists for many years but good data are not available on this point. Unfortunately, neither egg nor mouse antigen content can be measured satisfactorily, so that the skin test cannot be standardized adequately. Negative skin tests are encountered frequently in the presence of serum antibodies. Occasionally, we have observed a positive test in the complete absence of antibodies. If this test has any real value it is for surveys rather than in the diagnosis of an individual case.

As is true of serologic methodology in general, two sera should be examined at least 2 weeks apart in order to determine whether the titer is rising, stationary, or falling. Single determinations are not very helpful unless negative, and then only if 3 or more weeks have elapsed since the onset of symptoms. Passive transfer antibody persists in undiminished titer for 2 to 3 months, but after that it decreases sharply.

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THE DISEASE

The spectrum of clinical expression of infection by *T. gondii*, although incompletely understood, has been expanded considerably in recent years. Basically, it may be divided into two categories: congenital and acquired.

Congenital Toxoplasmosis.—This type was the major source of interest for a number of years because it was the first human infection proved to be caused by Toxoplasma. This can be a very serious disease whose outcome may be stillbirth or neonatal death; neonatal illness manifested by jaundice, splenomegaly, hepatomegaly, rash, and lymphadenopathy; or residua such as chorioretinitis, cerebral calcification, hydro- or microcephaly, psychomotor retardation, or convulsions. Infants so afflicted seem to represent unique experiences, for there are no authenticated cases of more than one pregnancy resulting in this complication in the obstetrical lifetime of one woman. It is generally assumed that congenital toxoplasmosis occurs as a complication of a primary infection that fortuitously was acquired during pregnancy. During the resultant parasitemia a necrotic focus may develop in the placenta, from which the fetus subsequently becomes infected.

In the immediate postpartum period, the mothers invariably have very high dye-test titers, substantial amounts of complement-fixing antibodies, and negative skin tests. The infant's antibody titers approximate the maternal level. Maternal skin tests are negative for about a year, which not only indicates that such sensitivity develops slowly but that the congenital infection is the result of a recently acquired maternal infection. It is of further interest in this regard that the mothers are usually quite young[20] and therefore more likely to be acquiring initial infections.

Cysts have been demonstrated[21] in a human uterus which was obtained during a routine autopsy. This lends further evidence of the dissemination and persistance of Toxoplasma even after an infection of a clinically undetected nature. The relation of this phenomenon to the congenital transmission of toxoplasmosis remains obscure, especially in view of the strongly suggestive serologic evidence that maternal infections in such cases are of recent origin.

Often all serologic examinations of the fathers are entirely negative,[20] making it unlikely that human-to-human transmission occurs with any degree of regularity except from mother to fetus.

Acquired Toxoplasmosis.—This may be either inapparent or overt, but the former has been thought to constitute the bulk of infections, probably reflecting our clinical limitations. It is quite likely that the future will see a diminution in the ratio of the two forms. Little appears to be gained from the use of more complex clinical classifications.

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The manner in which man (or, for that matter, animals) acquires infections with Toxoplasma is not known; regardless of how it comes about, parasitemia appears to occur and play an important role in the subsequent events. The latter may be confined to a major tissue system, resulting in a predominance of the appropriate signs and symptoms. Multiple involvements, however, may occur in any one person. Few symptoms seem to accompany the acquisition and early dissemination of the organism, but the onset of symptoms may coincide with the appearance of a maculopapular rash. This may persist for 1 to 3 days, suggesting the diagnosis of rubella, especially if lymphadenopathy is present. The latter may be the predominant clinical finding. In other instances encephalitis has been noted (with or without rash), in which case organisms may be demonstrated in the spinal fluid both directly and by mouse inoculation.

There may be generalized muscular pains and aches at the onset or subsequently. These probably reflect invasion[22] of skeletal muscle where organisms have been demonstrated in biopsy sections, at postmortem, and in mice that were inoculated with the tissue. There may be profound weakness with involvement of the myocardium and clinical evidence of myocarditis. Pulmonary symptoms may be prominent[23,24] and diffuse involvement of the lungs by parasites has been demonstrated in a few instances (this is not known to result in calcifications). It is possible that spread to the eye occurs during the parasitemia, but uveitis has been noted only with rarity during clinically recognized acute toxoplasmosis.

A number of detailed case reports of acquired toxoplasmosis have been published[22,23,25-40] in various parts of the world. While the references cited do not represent the total of recognized cases, they are illustrative of the experiences that are being recorded at an increasingly rapid rate. Some of the patients acquired their infections in laboratory accidents,[27,30,33,35,36] which emphasizes the hazards of exposing nonimmune persons to Toxoplasma. The aggregate of this experience permits certain generalizations that may be of assistance in dealing with an individual diagnostic problem. First, infection of lymph nodes with enlargement but without suppuration is common. This may be more prominent in one chain or gland than in others. Lymphadenopathy can be quite painless

and unaccompanied by any systemic signs such as fever, weight loss, etc. It may be of short duration or persist for months. "Asymptomatic lymphadenopathy" may be the commonest form of acquired, clinically expressed toxoplasmosis. On the other hand, lymphadenopathy may be accompanied by fever with or without apparent involvement of other systems; splenomegaly is uncommon. The Paul-Bunnell test is uniformly negative, although the clinical diagnosis of infectious mononucleosis is frequently considered. Siim[28,37] has reported 2 cases in which months after acute toxoplasmic lymphadenopathy the patients acquired typical infectious mononucleosis with positive heterophile tests. He has studied approximately 200 cases of acute toxoplasmosis in which lymphadenopathy predominated.[41] Of 38 of these with dye-test titers of 1:1,250 or more, parasites were isolated from 28 by inoculating lymph node suspensions into mice. On the other hand, no parasites were isolated from 44 patients with titers of less than 1:1,250. All had negative Paul-Bunnell tests, splenomegaly was most unusual, and there was no severe pharyngitis such as may be seen in infectious mononucleosis. The atypical lymphocytes observed in the peripheral circulation were not those characteristic of infectious mononucleosis.

The rash is generally maculopapular (petechiae have been noted) in type and may appear at the onset (or some days later) of the clinical illness. It has not been found to involve the palms, soles, or scalp and it is not pruritic. The mechanism of rash production is unknown, although it is thought to reflect spread of the organism throughout the host.

Acquired toxoplasmosis may concentrate on the central nervous system to produce meningoencephalitis. This is not necessarily fatal; spontaneous, complete recovery has been observed. The cerebrospinal fluid may contain few or many cells which are generally mononuclear in type. Delirium, convulsions, and coma, as usual, are ominous signs. There is one report[40] of a patient who had a space-occupying cerebral lesion that proved to be a toxoplasmic granuloma.

All or any of the above may be combined with severe, generalized muscle pains (skeletal muscle lesions), polyarthralgia, pneumonitis, weakness, lassitude, myocarditis, chills, sweats, remittent high fever, and weight loss. Yet recovery may be complete. Convalescence is usually prolonged in proportion to the severity of the illness. The total leukocyte count is usually normal or moderately depressed, but granulocytopenia, eosinophilia, and/or atypical lymphocytes may be seen.

Although the unpredictable nature of the clinical course as we now know it makes prognosis and the evaluation of therapy most difficult, most patients appear to recover completely.

In the acquired cases, dye-test antibodies appear to be produced rapidly, with high titers generally measurable approximately 2 weeks after the onset of symptoms (the incubation period is not known in man except in a few laboratory-acquired infections). Complement-fixing antibodies require an additional 2 weeks or so to appear, but the hemagglutination test becomes positive several days after the dye test. Because complement-fixing antibodies develop more slowly than dye antibodies, the dye test may be markedly positive at a time when complement-fixing antibodies are absent. By the same token, complement-fixing antibodies tend to diminish more rapidly than dye antibodies, so that 2 to 3

years after an infection one may again find very positive dye and negative complement-fixation tests. Therefore, the occurrence of high titers of dye-test antibodies and negative complement-fixing tests may indicate either early infection or late convalescence. To resolve this question, several sera should be examined at intervals of several weeks or a month; if no complement-fixing antibodies appear, then it is quite likely that one is dealing with a recovered individual, rather than one who is acutely ill. The reverse situation would be diagnosed if complement-fixing antibodies appeared in the repeat examinations.

The case fatality rate for acquired toxoplasmosis is unknown since the attack rate has not been measurable. It appears as though relatively few persons die of the acute, acquired form of the disease, but full recovery may be delayed. Six months to a year or more may be required before the individual can regain his full working capacity.

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TREATMENT

It was demonstrated by Sabin and Warren[42] that sulfathiazole and sulfapyridine could suppress Toxoplasma infections in mice. Subsequently, a number of other agents were reported to have antitoxoplasmic activity, but the most effective and commonly employed therapeutic measure is the combination of sulfadiazine and pyrimethamine which was first described by Eyles[43] who has reviewed his experiences extensively. He found the most active sulfonamides to be sulfadiazine, sulfamezathine, sulfamerazine, and sulfapyrazine, but that a substantial increase in therapeutic benefit is achieved by combining one of these with pyrimethamine. The various antibiotics were relatively ineffective, as were other sulfonamides.

When employed clinically, the sulfonamide selected should be administered in regular therapeutic dosage. The optimal dose of pyrimethamine (Daraprim), however, is not certain and has been determined only empirically. During the first 2 to 7 days the maintenance dose is doubled, and then reduced subsequently. Adults and large children may be maintained on 25 mg. per day, but those weighing less than 60 pounds may be treated according to the ratio of 25 mg./60 pounds. A reasonable period of treatment is 1 month; unless some improvement is apparent during the first week or two, little more is to be expected in subsequent weeks.

Leukocyte counts should be performed frequently, since either drug may produce reactions; this is especially true for pyrimethamine, which is an antifolic agent capable of producing marked leukopenia and thrombocytopenia. If the latter is severe, treatment should be stopped or folinic acid[44] added to the regimen to counter the undesirable hematologic effects of the pyrimethamine.

There are a number of reports[8,39,45,46] of the treatment of acute systemic toxoplasmosis or uveitis (presumed to be of this origin) with the sulfonamide-pyrimethamine combination. Immediate benefits appear to be real, though the clinical course of the disease is unpredictable. If fever is present it usually disappears in a day or two. Lymphadenopathy seems to regress more quickly and eye symptoms tend to lessen. Unfortunately, it appears unlikely that encysted

organisms are any more affected by the drugs than by antibody. In one case[39] live organisms were demonstrated by mouse inoculation with a lymph node suspension obtained 66 days after completing a course of therapy with what appeared to have been good results. It might also be reasoned from this experience that clinical symptoms are dependent upon the presence of actively multiplying Toxoplasma which are susceptible to combined drug therapy, in contrast with encysted organisms which may neither produce clinical symptoms nor be affected by the medication. This point of view is consistent with the opinions of others.[39,47] Much remains to be learned of the action of these drugs; for example, Cook and Jacobs[48] found that pyrimethamine eradicates proliferating parasites in tissue cultures, but no direct activity by either sulfadiazine or pyrimethamine, alone or in combination, has been demonstrable by in vitro metabolic experiments in our own laboratory.[49]

The selection of patients for treatment may present a problem. This is particularly true when the patient is an infant. It is our own opinion that if the baby is considered to have an active infection treatment should be instituted. One should not expect damaged tissue to restore itself to normal function, but treatment may prevent further injury to vital centers. Acquired acute infections, also, ought to receive treatment. In the case of uveitis, if Toxoplasma has not been eliminated as the causative agent, this, too, might benefit from a course of drug therapy. It should not be forgotten that the sulfonamide-pyrimethamine combination is a very potent one, that other infectious agents may be affected by it, and, consequently, that a good response does not prove that the patient has active toxoplasmosis.

There are several schools of thought as to how toxoplasmic uveitis may be produced. One group believes that it is due to active infection and that the parasites are multiplying, in which case chemotherapy would be expected to exert a mediating influence. Others are of the opinion that the active uveitis (and recurrent episodes) results from the spontaneous rupture of a cyst which leaks antigen-containing fluid to produce a local hypersensitivity reaction. Since such patients already have antibodies, it is unlikely that organisms released from the cyst could multiply to a significant degree. Thus, if the symptoms are due to local allergy and not active infection, it would be reasonable to expect a better response to treatment of the tissue reaction than to an attempt to eradicate the parasites. In the former, steroids might be of benefit. Indeed, some patients with uveitis presumed to be of toxoplasmic origin have benefited from steroid therapy. At present we have no clinical method for determining which of the two mechanisms is operating in a given patient, nor are we certain that either is the correct pathogenetic explanation of uveitis.

EPIDEMIOLOGY

The only Toxoplasma infections whose origins are known are those of congenitally infected infants or those following laboratory accidents or cannibalism by animals. The organism is widespread throughout the world[50] and evidence of infection has been found in many species of animals and birds, par-

ticularly domesticated ones. It is often assumed that the demonstration of antibodies in an animal associated with a human case identifies the animal as the source. There is no evidence that this is more than an assumption which still remains to be proved. There are others who feel that humans transmit infection to other humans, and in one instance the organism was reported to have been isolated from human saliva.[51] The problem is complicated by the common experience of not finding antibodies in the husband, when studying families in which a congenital infection has been found, at a time when the wife (and mother) has high titers by the various serologic procedures. One would expect transfer between wife and husband to take place if human-to-human infection occurs with any degree of frequency. The fact that two or more members of a family appear to have had recent infections may indicate nothing more than that they were commonly exposed to a single source.

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The following is a good example of the problems encountered. Recently, a male patient was admitted to the hospital because of severe, diffuse myocarditis. His serologic data indicated that he had acute toxoplasmosis, although an attempt to isolate organisms from a skeletal muscle biopsy failed. The wife, who was well at the time, was also investigated and found to have extremely high titers of dye and complement-fixing antibodies. When questioned closely, she recalled having noted cervical adenopathy some weeks previously, approximately at the time her husband developed his first symptoms. Thus, it would seem that the husband and wife, one with overt clinical illness and the other without, were infected at a common source. There were no children. A cat belonging to the family was found to have a low titer of antibodies by the dye test. The relationships between these factors are obscure but typical of the problems of tracking down the source of infection.

It has been said that the occurrence of cervical adenopathy indicates that the infectious agent is orally acquired by man. Some recent data may be of interest in this regard. It was suggested several years ago that, because animals could be infected as a result of cannibalism and since swine frequently have antibodies for Toxoplasma,[50,53] the ingestion of undercooked meat might be the source of human infection. Several recent epidemiologic studies have been concerned with this question. One contrasted the prevalence of antibodies among the general population of New York City with that found among orthodox Jews who had never eaten pork products.[53] The evidence of infection was similar in both. Another study, conducted in India, contrasted the antibody levels of vegetarian Indians with those of meat-eating Indians.[54] Here, again, the prevalence of antibodies appeared to be similar in both groups. Not only have wild rabbits, also vegetarians, been found to have Toxoplasma antibodies, but epidemics of toxoplasmosis have been reported among them in Denmark.[55]

Jacobs and his group have shown that not only are Toxoplasma that are contained in cysts more resistant to acid-pepsin than are proliferating parasites, but that transmission to animals by cannibalism occurs only when the carcasses contain cysts.[56] From these and other data it seems reasonable that infected meat may be a source of infection, although they do not explain the presence of antibodies among those who do not eat meat.

It has been suggested on occasion that insects can transmit infections, but this has not been proved. On the basis of our own studies of congenital cases, infections may be acquired during any month of the year, which would preclude some insect vectors.

SUMMARY

The past decade has witnessed the evolution of *Toxoplasma gondii* from a laboratory curiosity to a secure position among the causative agents of human and animal disease. The distribution of the parasite is world wide and it has been demonstrated in many mammals and birds. Most infections appear to be mild or inapparent, but severe (and even fatal) damage may be observed in human fetuses or newborn infants. Fatal illnesses may be contracted by children and adults but, fortunately, this is uncommon. Lymphadenopathy occurs often enough in acquired toxoplasmosis to be incorporated in the clinical differential diagnosis of diseases of the lymphatic system. Neither the attack rate for clinically apparent cases of toxoplasmosis nor the case fatality rate can be estimated at this time.

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TREATMENT OF HYPERTENSION

A 23-Year Follow-Up of 453 Patients With a Selected Review and Report of Current Experience

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THIS is the fourth and final report on 453 medically treated patients with hypertension, since there now are only 79 survivors. The majority were seen first in the years 1935 to 1940. No new patients have been added to the series since 1941. All patients were personally observed and followed. For the purpose of follow-up, original classification has not been changed, having been made after a year or more of observation, except in Grade IV, since these patients are classified on recognition of papilledema. The classification is as follows: Grade I, hypertension without recognized organic changes or function failure; Grade II, no function failure, but with organic changes in one or more of the three vital areas—head, heart, or kidneys; Grade III, organic change plus function failure in one or more vital area; and Grade IV, the clinical syndrome of malignant hypertension, the diagnostic sign of which is papilledema.

The latest of three prior reports reached these conclusions[1]: The validity of this classification is demonstrated. The relative risk at younger ages is greater and decreases rapidly with age. Mortality is lower for women, except in Grade IV. There is an increase in age from Grade I to Grade III indicating that each grade is, to some extent, a later development of the previous one. Duration of hypertension, apart from advancing age, has little effect on mortality except in Grade IV in which short duration is associated with higher mortality at youngest age. With each increase in grade, patients die at an increasingly faster rate than the general population. Survival ratios relative to the general population follow simple patterns, permitting a basic prediction of survival in each grade. These basic conclusions have been confirmed by other comparable studies.[2,3,4]

Preliminary statistical treatment of these data generally confirms previous conclusions except that expectancy for younger females is about the same as for males in Grade I. This report presents 17-year survival curves since closing the series to additional patients (Table I, Fig. 1) and emphasizes in a 23-year over-all follow-up study the cause of death (Table II), namely vascular disease in head, heart, or kidney, which accounts for the death of three-fourths of those originally

TABLE I. CLASSIFICATION* ACCORDING TO RECOGNIZED ORGANIC CHANGES IN HEAD, HEART, AND KIDNEYS OF 453 PATIENTS WITH ESSENTIAL HYPERTENSION—SEX, NUMBER, AND PER CENT OF SURVIVORS 17 YEARS AFTER CLOSING THE SERIES TO NEW PATIENTS IN 1941

	GRADE I		GRADE II		GRADE III		GRADE IV	
	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE
Living	15	30	4	17	2	9	0	2
Dead	26	39	23	44	97	93	32	20
Per cent of survivors								
Each sex	37%	43%	15%	28%	2%	9%	0%	10%
Both sexes	41%		24%		5%		4%	

*See text for classification.

TABLE II. CAUSES OF DEATH BY PER CENT ACCORDING TO GRADES

	HEAD	HEART	KIDNEY
Grade I	37	37	3
Grade II	35	30	9
Grade III	35	42	14
Grade IV	23	23	48

Remainder died of subarachnoid hemorrhage, pulmonary embolism, mesenteric artery thrombosis, rupture of aortic aneurysm, and of unrelated causes—cancer, tuberculosis, rheumatic heart disease, gastrointestinal hemorrhage, suicide, accident, or cause unknown (6 to 7 per cent). Two Grade IV patients were found to have glomerulonephritis.

Like other persons, patients with hypertension may show vascular aging other than in the three vital areas, may have congenital vascular defects, and are subject to the usual diseases and fatal hazards both physical and psychic. The chances of fatal conditions, other than cardiovascular renal, are 1 in 4 for those with the milder Grades I and II hypertension, about 1 in 10 for the severe Grade III with shorter expectancy, and approximately 1 in 20 for Grade IV, the group with the shortest life expectancy.

graded I or II and 90 per cent of those graded III. The proportion of deaths from cerebral and cardiac causes is less (46 per cent) in Grade IV because of the larger proportion of renal deaths presumed due to renal vascular spasm and consequent vascular necrosis, i.e., the pathologic syndrome of malignant hypertension.

In the general population cardiovascular renal disease accounts for a little over one-half of the total mortality.[5] Ninety per cent of these cardiovascular deaths are due to hypertension and arteriosclerosis. Therefore, what we have been following and what we should be treating is arteriosclerotic or atherosclerotic vascular disease in patients who also have hypertension and in whom vascular aging appears oftener and kills sooner than in the general population. The treatment problem in hypertension is not only of the blood pressure level and

participating intravascular trauma, but also of the eventual atherosclerosis and its thrombotic complications. The blood pressure level is the prime killer in the relatively few cases of Grade IV malignant hypertension. As this and other long-term follow-ups demonstrate, some patients may have high blood pressure and live the normal length of life in good health. I have found that (a) family history of longevity and relative freedom from vascular disease until late in life in the individual hypertensive patient's siblings and forebears, (b) a variable unsustained hypertension, particularly of the diastolic pressure in the patient, and (c) freedom from recognizable vascular disease indicate a favorable prognosis, and their opposites an unfavorable one. Women have a more favorable prognosis than men. The kind and amount of treatment may be adjusted to probable life expectancy as indicated by survival curves for each grade. But the mortality statistics of the general population indicate the need for prospective treatment of degenerative vascular disease at the earliest sign of this possibility. One such sign is persistent hypertension. This finding in most instances is an indication for the least harmful, cheapest, and most effective prophylactic treatment of atherosclerosis and blood pressure level, namely, a diet restrictive in fat and salt. This diet however, is also the most difficult for both doctor and patient.

I have reviewed nearly ten pounds of print in the form of articles, abstracts, reviews, and brochures, numbering more than 350 communications, and have consulted my current experience in the office treatment of the blood pressure level and of vascular disease associated with it. The following are my conclusions with references to those reports which seem most significant.

TREATMENT OF BLOOD PRESSURE LEVEL PRIMARILY BY DIET, SUPPLEMENTED BY HYPOTENSIVE DRUGS

Salt restriction for hypertension was recommended 55 years ago,[6] demonstrated as effective nearly 40 years ago by Allen,[7,8] then investigated by a few,[9,10] rediscovered in the treatment of kidney disease, and temporarily popularized for the treatment of hypertension by Kempner 15 years ago.[11] The role of dietary sodium as a contributing cause of hypertension, its restriction as an effective treatment, and the safety of long-term restriction recently has been documented by Dahl.[12,13]

Learning of Allen's and O'Hare and Walker's work while still in medical school, I determined to restrict the salt intake of patients with hypertension and have done so for 30 years of practice. I prescribe a 200 mg. low sodium diet in about one-fifth of the hypertensive office patients whom I see. Seventy-five per cent have mild or moderate Grade I or II hypertension. One-third of these follow the diet strictly, an additional 50 per cent fairly well. One-fifth of all patients show a fall of blood pressure to normal or near-normal limits.* Supplementary hypotensive agents are used in those who do not follow the diet or fail to show a satisfactory fall in blood pressure. In Grade III hypertension and all obese patients in Grades I and II, I prescribe a low fat, low sodium, 900 to 1,000

*I choose to call normal 140/90 in young adults, 150/100 at middle years. Near normal is defined by me as 150/100 in young adults, 160-170/110 at age 50 and beyond.

calorie diet. This diet is used in one-half of the patients I see. One in 10 follows the diet strictly, about one-third fairly well. One-third of all patients achieve normal or near-normal blood pressures but only 15 per cent require no hypotensive drugs. Seventy per cent of the patients for whom this diet is prescribed have severe Grade III or malignant hypertension. Because of the severity of their disease, hypotensive medication may not be withheld. Rice diet, initially for acute cerebral or heart impairment and for papilledema, is prescribed in about 15 per cent of the patients I see, with excellent initial and later fair adherence in 45 per cent and good hypotensive effect in 60 per cent. Hypotensive medication is always used for these severer grades. Normal or near-normal blood

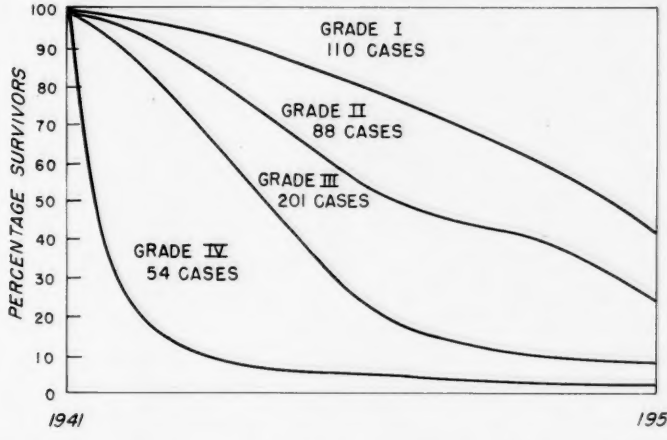

Fig. 1.—Percentage of survivors by grade since closing the series to additional patients in 1941, most of the patients having been first studied between 1935 and 1940. The majority of Grade IV patients, without prolonged rice diet or sympathectomy available at that time and without the hypotensive drugs now available, died in less than 2 years. In this group the median duration of known hypertension was 1.5 years, and the time of actual observation in this study prior to death was slightly over 4 months.

pressures are achieved in slightly over 25 per cent.[14] Hypotensive effects may not be precisely allocated between diet and medication, except, in general, the more strict the dietary adherence, the less medication is required. The severity of the disease and the ability or willingness of the patient to follow the diet are the controlling factors.

THE USE OF DRUGS* IN THE TREATMENT OF THE BLOOD PRESSURE LEVEL

Since impairment and death from vascular disease comes earlier than average for patients with hypertension, the blood pressure level should be controlled. Diet reduces the amount of drug treatment, increases the effectiveness

*Acknowledgment is made to Ciba Pharmaceutical Products, Inc., Merck, Sharpe & Dohme, and E. R. Squibb & Sons for various hypotensive agents, often with matching placebos for preliminary clinical trials of Rauwolfia serpentina, its fractions and derivatives and chlorothiazide and its modifications, also to 53 other manufacturers or distributors who have supplied me no less than 100 different preparations, two-thirds of them Rauwolfia serpentina often in combination with as many as three or four additional drugs.

of milder drugs, lowers the necessary dose of stronger drugs, and permits omission of all drugs in some cases. The decisions we must make are: at what blood pressure level hypotensive drugs are indicated, which ones to use singly or in combinations, and in what order.

Considering the blood pressure level alone, insurance statistics for many years have demonstrated that mortality increases progressively with increasing blood pressure over a level of 140/90.[15] This has led to the suggestion by life insurance physicians that the ideal blood pressure is the lowest one compatible with normal physiologic function.[16] This suggestion helps the selection of preferred risks and doubtless, if adopted, would increase the practitioner's case load of hypertensive patients. Treatment by hypotensive drugs has been implied as necessary for levels over 150/100,[17] while diet as treatment for the blood pressure level in obese hypertensives has been minimized.[18]

I disagree with these opinions. In the absence of marked organic change or function failure, mortality becomes significantly increased with sustained blood pressures of over 200/110-120, particularly in respect to the diastolic pressure, this being especially notable in men.[2,3] I use hypotensive agents when phenobarbital and diet do not lower the pressure below 180/110 in men, allowing a little higher pressure in women aged 45 years and over and when patients do not follow their diets. My objective is to achieve a blood pressure range of 150-170/100-110. In men and women under 45, I use hypotensive agents in addition to diet and phenobarbital to obtain a blood pressure of 150/110 or less. These levels refer to the peaks, i.e., the maximum levels at home under circumstances of stress and particularly at office visits, when blood pressure levels almost without exception are higher than home pressures.

CURRENT DRUG TREATMENT OF HYPERTENSION

Less than one article in ten reporting on drug treatment of hypertension reveals in detail the number of patients who refused treatment or were lost from follow-up, or whose drug reactions required the withdrawal of treatment, or who died or suffered serious vascular accidents while under treatment. These eventualities may total from 10 to 20 per cent and sometimes up to 50 per cent on polypharmaceutical treatment. To put it as generously as possible, the manufacturers' brochures are as enthusiastic as the most enthusiastic of their clinical investigators.

The ganglionic blocking drugs are pharmacologically the purest, the most numerous, most effective, and most dangerous hypotensive agents. Hexamethonium has been largely superseded by the longer-acting pentolinium which, in turn, is being displaced by the still longer-acting chlorisondamine or the much better-absorbed mecamylamine. The position of these may be threatened by still newer preparations under investigation. The virtue of these drugs is also their fault, i.e., drug-induced hypotension with its consequences in cerebral, coronary, and renal circulation and parasympathetic paresis (glaucoma, paralytic ileus, pyloric obstruction, urinary bladder atony, impotence). These effects are potentiated by infections, environmental heat, and alcohol. Mecamylamine is

thought to be a modifier rather than a competitor of acetylcholine. It may cause severe peripheral and central nervous system toxicity: flapping tremor, hyperreflexia, hallucinations, delusions, convulsions, and psychoses. I use it cautiously in the smallest possible dose in conjunction with diet, have not encountered serious toxic effects, and obtain a sustained hypotensive effect with 1.75 to 5 mg., rarely 7.5 mg., at 12-hour intervals. It should not be used in patients with nitrogen retention.

When appropriately used, prevention of heart failure is the triumph of ganglionic blockade. In acute episodes, too often due to the physician's or the patient's own neglect, these drugs may be life-saving and clearly are superior to prior methods. Prevention of cerebral thrombosis or hemorrhage is doubtful except for subarachnoid hemorrhage. Prevention of coronary thromboses and relief of chronic coronary insufficiency by ganglionic blockade also are doubtful, these drugs being contraindicated in acute episodes and only to be used with the utmost caution in chronic states of this sort. I obtain nearly perfect sustained control in 1 of 5 patients, definitely lower but variable levels in 60 per cent, and I do not attempt to obtain strictly normal or near-normal levels in the patients, usually Grade III, who have evidence of cerebral or coronary circulatory insufficiency. Established renal failure, unless secondary to cardiac failure, is not helped. Twenty per cent of patients stop taking these drugs because of the detailed supervision required or because of side effects. I have 6 patients taking daily home blood pressures and reporting by blood pressure charts. One of these travelled to Australia for 6 months, reporting with blood pressure charts and being advised by air mail, finally returning in better condition than when he departed. In general, it seems that effective use of ganglionic blockade is not too widely accepted by either patients or practitioners. Physicians tell me that its use is for teaching hospitals or veterans' clinics where time is unimportant to physicians and cost unimportant to patients. Hoobler's survey confirms this.[19]

Antiadrenergic and adrenolytic drugs have no place in treatment of the blood pressure level, may have a place as screening test substances for pheochromocytoma, although I use urinary catechol determinations since they are probably more accurate and no more expensive in time and money. Veratrum and its derivatives have little use, unless protoveratrine A proves to have a wider margin between therapeutic and toxic effects than previous preparations, a possibility which seems unlikely. I have one patient taking protoveratrine A. The same meticulous adjustment of dose to avoid toxic effects is required. Hydralazine is too weak in hypotensive action and too powerful in serious toxicity (about 10 per cent) to justify its use other than in exceptional instances. Only two of my patients are taking hydralazine, along with other hypotensive agents.

Rauwolfia serpentina, its various fractions, and more or less pure active principles provide a hypotensive action actually no better than phenobarbital[20] or at best only slightly more potent and with more side effects than phenobarbital, as demonstrated by a statistical evaluation of an adequate sampling of ambulatory patients for a sufficient period of observation while on alternating prescriptions of placebo, phenobarbital, and the alseroxylon fraction of Rauwolfia serpentina.[21]

My double-blind placebo studies of Rauwolfia serpentina and various of its fractions[14,22] and of other Rauwolfia preparations, including Syrosingopine, have demonstrated a mild hypotensive effect in 20 to 25 per cent, plus a sedative effect and frequent but usually well-tolerated other side effects. In patients such as an engineer, a scholarly bookseller, or a research director, for example, namely, the exceptional persons who use their brains to maximum capacity, a slowing of mentality is the most annoying effect and may require giving up the drug. Evidently it is the very effect most cherished by the majority of patients, therapists, and manufacturers. This explains the habit manufacturers have of including Rauwolfia or other tranquilizers in their trade-named combinations. Other reported side effects are: sodium retention, weight gain, peptic ulcer (two cases in my experience), and severe depression requiring shock treatment. In the majority of ambulatory hypertensives, I prescribe phenobarbital with belladonna or a nonsodium antacid if indigestion is a complaint. The basic prescription is a 1,000 calorie, low fat, low sodium diet. Often this is highly effective. Fig. 2 illustrates the favorable effect of diet plus phenobarbital on the blood pressure, followed by weight regain when the patient omitted treatment. He then suffered a cerebral accident. The latter motivated him to follow strict treatment, this time requiring hypotensive medication in addition to diet. By maintaining normal weight and good dietary self-discipline, patients with Grades I and II hypertension often are gradually able to do well without sedatives or hypotensive drugs.

Chlorothiazide, the most recent and most popular hypotensive drug, and its modifications are continuously powerful oral diuretics. In short trials it increases sodium, potassium, and water excretion, the peripheral resistance, and the hematocrit, while lowering glomerular filtration rate and the blood pressure. Nitrogen may be retained, especially in patients with poor renal function. These effects in comparable doses are similar to those of mercurial diuretics and probably account for the hypotensive action although a pure hypotensive effect, mechanism not as yet determined, is claimed. If the hypotensive action is due to the diuretic action, as physiologic effects indicate to competent observers,[23] unfavorable long-term effects on the kidneys are possible. During observation many years ago of mercurial diuresis in hypertensive patients without cardiac or renal dysfunction, I noted the production of transient proteinuria and increased excretion of red cells in the urine. This has cautioned me in the use of diuretic agents. A recent report shows that uric acid may be elevated by chlorothiazide, apparently precipitating gout in a predisposed patient. Also noted was that in the production of goutlike symptoms the intensity of this effect is not necessarily in direct ratio to the height of the uric acid level in the blood.[24] This production of joint pain unhappily reminds me of the effects of hydralazine which began to appear with the use of the drug after a year or more.

I have used chlorothiazide for various periods in 42 patients with hypertension and without heart failure. One has had borderline renal failure and one frank uremia. Twelve were Grade III; 3 who were formerly Grade IV regressed to Grade II or III by the use of diet, Rauwolfia, veratrum, or ganglionic blockade prior to the use of chlorothiazide. The others were mostly Grade I, but with high

sustained blood pressure levels. In all, 14 patients were on ganglionic blocking drugs. Chlorothiazide was the only drug used in 4. Low fat, low sodium diet was prescribed in all. Normal blood pressure of 140/90 or less was achieved in 7, near normal (150/110 or less) in 12, and a definite fall in 9 more. In 4 I omitted the drug as no longer necessary. Eight persons discontinued treatment; effect was doubtful in one, and no significant blood pressure fall has been obtained in one cooperative patient. In another severely ill patient refractory to all hypotensive medication, chlorothiazide has been no more helpful than the others.

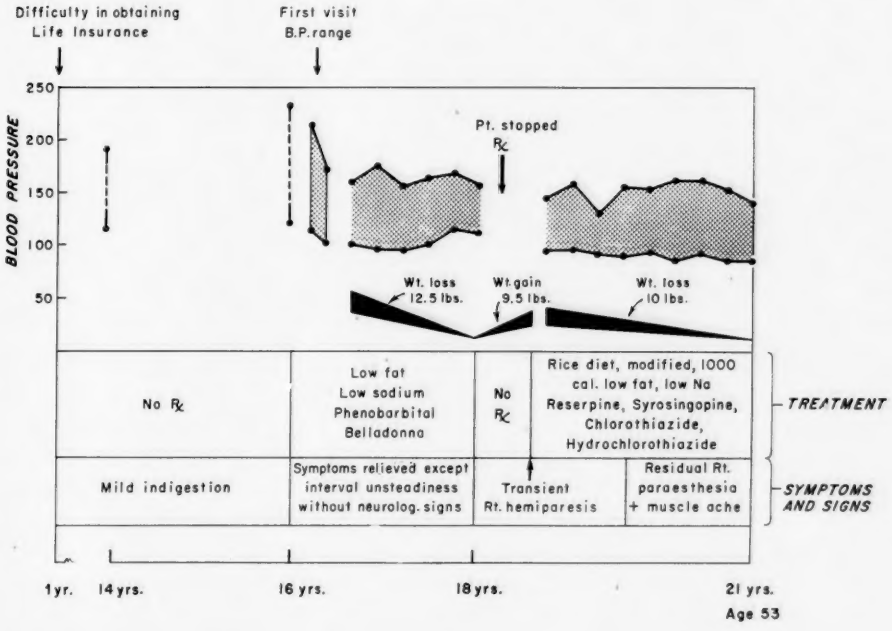

Fig. 2.—Mild Grade I hypertension evidently present over 16 years, without symptoms referable to hypertension itself. Subjective unsteadiness may have been due to phenobarbital or to developing cerebral circulatory insufficiency though repeated neurological examinations were normal. Increase of years, regain of weight, and persistent mild hypertension seemingly culminated in a small cerebral thrombosis. Prompt recovery was associated with rice diet, later modified gradually to a low calorie, low fat, low sodium diet with hypotensive medication.

Thus, in two-thirds of this group the hypotensive effect is unequivocal. All but 6 of these patients were treated with 0.5 Gm. of chlorothiazide or less. The most anyone received was 0.75 Gm. daily. Only one annoying hypotensive episode has been encountered. One patient experienced the low sodium syndrome and proved to have myxedema which was not at first recognized. Gastric intolerance has been exceptional and when present has been mild. Only one hemorrhagic phenomenon (petechiae) has been encountered. After temporary discontinuation, the drug was resumed without recurrence of petechiae. Melena and hematuria

have been reported as possible side effects.[25] Two of these patients have symptomatic gout with elevated uric acid. In one case, symptoms appeared for the first time, although an habitually elevated uric acid had been observed just before starting chlorothiazide. These symptoms were relieved by colchicine, and chlorothiazide was continued. In the other patient, symptomatic gout appears off and on but seems to have been worse while on chlorothiazide. Just recently routine checks of blood uric acid in patients have been started. Seven instances of elevated uric acid have been found ranging from slight (5.9 mg.) to considerable (9.8 mg.) elevation. One of these patients has slight to moderate nitrogen retention.

Some of these patients and other additional ones (40 in all) recently have been treated by hydrochlorothiazide, evidently with the same hypotensive effect in doses of 12.5 to 50 mg. daily. One patient has had leg cramps with a blood sodium of 140 mg./100 c.c. No other untoward reactions have been noted.

Early reports in the public press called chlorothiazide a major breakthrough in the treatment of hypertension. Subsequent medical articles report that the dose of ganglionic blocking agents may be reduced by 50 per cent in as many as one-third of patients, that all hypotensive agents were eliminated in a few, and that salt may be used in the diet. An equally good conclusion would be that chlorothiazide demonstrates again the effectiveness of dietary salt restriction alone in some cases and in reducing the amount of hypotensive drugs needed in most cases, a principle which I have long advocated and others have factually supported longer than I.

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THE CAUSE AND TREATMENT OF ATHEROSCLEROSIS IN PATIENTS WITH HYPERTENSION

Long-term follow-up of patients with hypertension clearly demonstrates that the 75 to over 90 per cent of deaths from degenerative vascular disease in such patients is 25 to 40 per cent higher than the normal expectancy of death due to this cause and that life expectancy is shortened.

There are plenty of conflicting reports in the literature from which to choose. The naive epidemiology of world-orbiting American clinicians intimates that the diets of materially favored people are the cause of degenerative vascular disease.[26] Local observers report that the medically famous, materially ill-favored Bantus are not exempt from aortic atherosclerosis even in younger ages.[27] According to their local Indian physicians, native East Indian vegetarians on a low fat diet are not free from coronary disease.[28] Some of the plain facts about ourselves and others and about the relation of fat intake to atherosclerosis and intravascular thromboses are these. All observers, including the sociologists, know that the "American child is fattened like some heifer meant for sacrifice."[29] Grown adults in college and Army camps are not ashamed to drink milk in copious quantities. In short, Americans overeat badly and suffer more than most others from atherosclerosis. The reason so many of my patients are unable to remain on a diet which they can feel is doing them some good is that they are unable psychologically to remain on a diet unless forced to do so by disabling consequences of atherosclerosis. When reproductive and aggressive satisfactions

abate in middle years, the only instinctive pleasure which remains for many of them is to eat and drink, watch activity, but not participate in it. Schroeder's careful critical on-the-spot observations in the Orient indicate that many factors are of importance besides fat, that there is still an inexplicable variation in the incidence of atherosclerosis and its fatal manifestations, a considerable variation in incidence of cerebral hemorrhage, and considerably less frequent thrombotic consequences in many Orientals than in people in the United States.[30] In the individual patient a detailed family history is a probability guide to his future since genetic factors appear to influence the incidence of hypertensive coronary disease and obesity,[31] although family and cultural habits of eating are difficult to separate from "heredity."

Allowing every reservation for other participating causes, there is no reasonable doubt that environmental agents contribute to atherosclerosis and that fat intake is the most important such factor—a fact known for 50 years, reemphasized over 20 years ago, and only now being rediscovered and elaborated. Animal fat intake as a cause of atherosclerosis practically satisfied Koch's postulates, recognizing that in certain higher animals and man a high total fat intake, particularly animal fats, increases the absorption of endogenous cholesterol, and that in animal and man there are strain and sex differences and modification by physical exercise.[32] Some evidence suggests that physical work may lower or at least prevent a rise of serum lipids, and therefore tend to prevent atherosclerosis. In a word, ingested fat may be less harmful if used up in heat and muscular work.[33,34] Aside from the long-term consequence of fat intake, there is the acute consequence of the single fat meal, namely, precipitation of thrombotic episodes.

Fat loading (a rich, fatty meal) plus physical indolence is not good for anyone and may be fatal in those patients, especially males over age 50, with a family history of hypertension, obesity, and coronary disease, particularly if the serum lipids are elevated and there are signs or symptoms of atherosclerosis already present. The reasons are: (a) angina pectoris has been induced 3 to 5 hours after fat ingestion in patients with known coronary insufficiency, at the peak of postprandial lipemia[35]; (b) whole blood coagulation time is significantly shortened 2.5 to 5.5 hours after a fatty meal in contrast to a low fat meal or no meal[36]; and (c) heparin injections will abate postprandial lipemia (turbidity of the plasma), the concentration of neutral fat, and the paper electrophoretic pattern of lipoprotein, and in fact *will relieve the induced angina pectoris and may reverse induced changes in the electrocardiogram and ballistocardiogram.*[37]

Oral gastric mucin is said to have a plasma-clearing effect similar to heparin[38] and sublingual heparin (1,500 I.U. of heparin potassium), while having no effect on the clotting mechanism, is said to clear postprandial lipemia.[39] I have tried this so far on three carefully observed hospitalized patients with cerebral circulatory insufficiency, one with transient hemiparesthesia, one with aphasia, and one with definite hemiparesis. Sublingual heparin did not alter plasma turbidity after fat loading or prevent one of the patients from developing an additional presumed cerebral thrombotic episode. Numerous reports state that 50 to 90 per cent of subjects taking 6 to 50 Gm. of sitosterol show a significant

lowering of serum cholesterol by preventing absorption of ingested and endogenous cholesterol.[40] Very large amounts of somewhat unpalatable liquid preparations or formidable numbers of more acceptable capsules, in either case incurring very considerable expense, are required. Spontaneous fluctuations of cholesterol, especially at high levels, over long periods throw reasonable doubt on the cholesterol lowering effect of these substances[41] as on the similar reported effect of large (3.0 Gm. daily) doses of nicotinic acid.[42] Radioactive fat tolerance tests may provide more accurate prediction of fat susceptible individuals and a better guide to effectiveness of treatment by diet restriction or unsaturated fat supplement or of plasma-clearing substances.[43] The following is a simple and practical demonstration for doctor and patient of plasma turbidity and the effect of fat meal. Samples of blood are drawn and allowed to clot, the serum is separated and centrifuged to remove any cells and to avoid subsequent hemolysis. Samples are taken on successive days fasting and after a generous fatty meal (cereal and coffee with heavy cream, bacon and eggs, toast and butter), and after a no-fat breakfast (fruit, cereal, coffee with skimmed milk, toast without butter but with jam or jelly). The fasting specimen and the one after the low fat breakfast are clear. After the fat breakfast, turbidity is marked and "cream" may be seen rising to the top. At the moment it seems to me as good a test of lipids in the blood as any, less expensive, and less bother than most.

It is evident to me that all patients with hypertension should be on a low animal fat as well as a low sodium diet. Unsaturated fats may be added and may be helpful, but obesity must be corrected if present by reducing calories. Garlic and other nonsodium condiments are advised and variety in the menu is urged. Certain substances may prove useful in clearing postprandial serum lipemia. Until they are proved to be of value, patients must be warned against heavy fat meals and advised to seek medical advice promptly if symptoms occur 2.5 to 5.5 hours after such meals. Physicians may be wise to have heparin at hand for parenteral use in emergencies.

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SUMMARY

This is the fourth and final report on 453 patients with hypertension, followed for 23 years, 17 years since closing the series to additional patients. Percentage survivals over the years are shown, demonstrating the usefulness of the original classification according to severity: Grade I = mild to Grade III = severe, and Grade IV = malignant. Cardiovascular renal disease is the cause of death in 75 to 90 per cent (as compared to 50 per cent for the general population) and appears earlier in life with each rise in grade.

It is safe, cheap, and often possible to control the blood pressure level by diet plus phenobarbital in Grades I and II and sometimes possible in Grade III. Drugs are easy to prescribe and are far more easily accepted by the patient than is restriction in diet. Rauwolfia serpentina and its fractions or derivatives are slightly, if at all, more effective than phenobarbital and have more side effects. The chief use of Rauwolfia is as a tranquilizer, rendering acceptable more rigorous drug treatment. Chlorothiazide is a substitute for salt restriction; the bulk of the evidence indicates that its mode of action is diuretic, depleting the body of

salt and water. The effect of years of use on the kidneys and other organs and tissues awaits further observation. This drug may cause a rise in uric acid and muscle and joint pains. Use of small doses is effective and recommended, combined with small doses of ganglionic blocking drugs in Grade III patients with actual or threatened congestive heart failure, and used alone in less severe grades with high blood pressure levels. Grade IV, clinically malignant hypertension with papilledema, requires every resource of diet and drugs to control the blood pressure level which by itself in this condition is rapidly fatal.

The ease with which the blood pressure level is observed and, in recent years, the ease with which it is effectively treated by a multitude of hypotensive drugs have misled many practitioners, and those who have presumed to teach them, to neglect the equally important therapeutic problem of patients with hypertension and also of the general population, namely, degenerative vascular disease. Patients with hypertension differ from nonhypertensives only by having it oftener and sooner. Degenerative vascular disease is related to age, hypertension, and unknown factors, as well as to ingested animal fat—the latter fact having been known for 50 years.

Evidence is presented that a basic treatment of all patients with hypertension is a low salt, low animal fat diet.

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ARE GEOGRAPHIC VARIATIONS IN DEATH RATES FOR THE CARDIOVASCULAR DISEASES REAL?

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IN recent years cause-specific mortality tabulations have been viewed with increasing suspicion. It has been argued that as the bulk of deaths moves from those produced by single demonstrable agents, such as tuberculosis, to those produced by a multiplicity of unknown or not easily demonstrable agents, such as the cardiovascular diseases, the accuracy and meaning of statements regarding underlying causes of death decrease.[1,2] To the extent that this statement is correct, it would appear that the detailed descriptions of causes of death as tabulated by vital statistics offices are less meaningful today than in the past.

Some critics suggest that all or nearly all of the geographic or temporal variations in death rates for such diseases as cardiovascular diseases or coronary heart disease simply reflect variations in the judgments of attending physicians as they select from a multiplicity of ill-defined causes that which "initiated the train of events that led to death."[3,4] It has also been recognized that inaccuracies may often result merely from failure to list available material correctly on the death certificate, from listing it in a way that causes improper coding, or from lack of sufficient clinical and laboratory data to determine accurately the underlying cause at the time the death certificate is completed.[5,6]

The purpose of this paper is to examine some evidence regarding the extent to which inaccuracies in cause-of-death statements and other factors may limit the usefulness of cardiovascular and coronary heart disease death rates for studying geographic variations in death rates within the United States. The need for studies in this area has been recognized[7,8] and some have already been made.[9,10,11] (The term *coronary heart disease* is used here to include all deaths classified in the International List of Diseases and Causes of Death as category 420, "Arteriosclerotic heart disease, including coronary disease.")

In view of large geographic differences in death rates for cardiovascular diseases and for coronary heart disease among white males in the age group 45 to 64 years and in order to simplify the presentation of data, only geographic differences in this particular age-sex-race grouping will be examined. Generally,

the observations made as to the usefulness of these death rates apply also to white females, ages 45 to 64. They probably apply to a lesser extent, however, to persons in order age groups. Among elderly persons it seems likely that the assignment of cause of death is considerably more difficult than among younger persons. As Starr has pointed out, no doubt elderly persons frequently die of causes unclear or unknown to the attending physician, and there is a resultant inaccuracy when an attempt is made to assign the death to a specific cause.[1]

Reasons for general interest in death rates for white males aged 45 to 64 years are that, since it is an age group with a substantial life expectancy, deaths in this age group constitute a substantial loss of productivity to society; and that death rates for cardiovascular diseases, particularly for coronary heart disease, are very high in this group, with white males aged 45 to 64 in the United States having a death rate for coronary heart disease approximately four times as high as that for white females and substantially higher than for white males in many foreign countries.[12]

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DEATH RATES BY STATES

Resident death rates for white males aged 45 to 64 vary considerably from one state to another for coronary heart disease, for all cardiovascular diseases, and for all causes, as is shown in Table I. Since the 20-year age span, 45 to 64, is rather broad, the rates shown have been age adjusted by 5-year age groups to the United States' total population. As a result, the states with a greater-than-average concentration of this population group in the 45 to 54 age bracket show a net increase in their age-adjusted age-specific rates; these consisted of the Southern and Southwestern States and California, Nevada, and Utah, as well as New York. These increases are in many instances nominal and the age-adjusted age-specific rates may be compared with ordinary age-specific rates.[9,15] (Through age adjustment to the entire population aged 45 to 64, the white male, age-adjusted age-specific rate in Table I is slightly less than the ordinary age-specific rate of 851.5 for cardiovascular diseases and 538.0 for coronary diseases.)

The remaining states had a slightly greater-than-average concentration of population in the 55 to 64 age bracket, so that age adjustment resulted in decreases in their rates, but generally less than 2 per cent. States with declines of more than 2 per cent were Montana, South Dakota, Nebraska, Iowa, and Minnesota. Three states showed increases in their cardiovascular disease death rates of more than 4.4 per cent: South Carolina, which already had the highest cardiovascular death rate, and North Carolina and Louisiana, which also had relatively high cardiovascular death rates. In general, there was very little correlation between the death rate and the amount of change as a result of age adjustment.

Variations by States.—For cardiovascular disease South Carolina has a death rate almost double that of New Mexico. The states with the lowest cardiovascular disease death rates are the Western Plains States, some of the Mountain States, and a group of South Central States (Oklahoma, Arkansas, Tennessee,

and Kentucky). It is of interest that these are largely rural states covering a contiguous area in the central portion of the country. The highest death rates appear in the northeastern states, other states with large metropolitan areas, and in some of the South Atlantic States.

Somewhat the same pattern appears for coronary heart disease. In this case the death rate is nearly twice as high in New York State as in North Dakota or New Mexico. The five states with the highest coronary heart disease death rates (New York, California, South Carolina, Rhode Island, and Massachusetts) all have rates 52 per cent or more higher than the five states with the lowest rates (New Mexico, North Dakota, Kentucky, Arkansas, and Tennessee).

At most, only a small portion of the marked variations in cardiovascular and coronary heart disease rates from state to state is due to chance variation resulting from the particular years selected. The states with rates ranking second highest and second lowest, for example, deviate from the United States rate five to ten times as much as the deviation to be expected if it were due to chance alone. Furthermore, ranks of published rates by year for cardiovascular-renal disease[16] show a very substantial consistency from year to year.

Validity of Differences.—Since cardiovascular diseases are charged as the cause of more than half of all deaths, variations in cardiovascular death rates have a marked relationship to death rates for all causes. For example, North Dakota is among those states with the lowest rates for both cardiovascular diseases and all causes of death, while South Carolina is among those with the highest rates. As a result, the death rate for cardiovascular diseases in South Carolina is only slightly less than the death rate for all causes in North Dakota. If the assumption is made that there are no real geographic differences and if North Dakota is assumed to have the same cardiovascular disease death rate as South Carolina, then the death rate for all noncardiovascular causes combined in North Dakota must be only 65.7 per 100,000 population as compared with the tabulated rate shown in Table I of 539.6. On the other hand, if it were assumed that South Carolina truly has the same death rate from cardiovascular disease as North Dakota, it would appear that the death rate for noncardiovascular causes is more than twice as high (or 643 points higher) in South Carolina than in North Dakota. If it is assumed that the true cardiovascular disease death rates for North Dakota and South Carolina lie between the death rates actually recorded for these two states, cardiovascular rates for both states must be 27 per cent in error (with a substantially greater error for the noncardiovascular causes). It would, therefore, appear likely that at least some of the difference is real.

A comparison of North Dakota with New York State reveals that the death rate from coronary heart disease in New York State actually exceeds the death rate in North Dakota for all cardiovascular diseases. As Table I shows, the death rate for coronary disease alone was 650.5 per 100,000 in New York, whereas the death rate was only 633.6 for all cardiovascular diseases in North Dakota. The North Dakota death rate for all cardiovascular diseases plus all deaths classified as "symptoms, senility, and ill-defined conditions, including sudden deaths," equals 647.2. Even if it is assumed that all of these deaths are in reality

TABLE I. AVERAGE ANNUAL DEATH RATES PER 100,000 POPULATION FOR SELECTED CAUSES, WHITE MALES, AGES 45 TO 64, AGE ADJUSTED, BY STATE, 1949 TO 1951*

GEOGRAPHIC DIVISION AND STATE	ALL CAUSES	ALL CAUSES EXCEPT CARDIOVASCULAR	DISEASES OF CARDIOVASCULAR SYSTEM (INTERNAT. LIST NO. 330-334, 400-468)		
			TOTAL CARDIOVASCULAR DISEASES	CORONARY HEART DISEASE†	ALL OTHER CARDIOVASCULAR DISEASES
UNITED STATES	1563.2	718.2	845.0	534.1	310.9
NEW ENGLAND					
Maine	1492.8	687.7	805.1	522.9	282.2
New Hampshire	1556.9	681.8	875.1	578.9	296.2
Vermont	1521.5	712.0	809.5	550.4	259.1
Massachusetts	1647.7	740.5	907.2	598.6	308.6
Rhode Island	1666.4	751.6	914.8	604.8	310.0
Connecticut	1536.3	706.8	829.5	551.6	277.9
MIDDLE ATLANTIC					
New York	1710.5	787.1	923.4	650.5	272.9
New Jersey	1703.9	763.9	940.0	584.5	355.5
Pennsylvania	1702.9	786.2	916.7	570.0	346.7
EAST NORTH CENTRAL					
Ohio	1533.6	706.2	827.4	529.8	297.6
Indiana	1505.1	667.5	837.6	522.1	315.5
Illinois	1696.1	760.7	935.4	534.1	401.3
Michigan	1557.6	727.1	830.5	537.4	293.1
Wisconsin	1358.4	607.4	751.0	477.9	273.1
WEST NORTH CENTRAL					
Minnesota	1261.1	563.8	697.3	442.4	254.9
Iowa	1249.9	550.4	699.5	451.2	248.3
Missouri	1471.2	714.5	756.7	450.2	306.5
North Dakota	1173.2	539.6	633.6	364.5	269.1
South Dakota	1201.1	555.3	645.8	422.1	223.7
Nebraska	1235.6	576.6	659.0	407.0	252.0
Kansas	1236.2	572.9	663.3	437.5	225.8
SOUTH ATLANTIC					
Delaware	1621.0	772.1	848.9	546.7	302.2
Maryland	1716.3	760.2	956.1	580.4	375.7
District of Columbia	1900.7	833.0	1067.7	622.8	444.9
Virginia	1542.2	671.0	871.2	537.0	334.2
West Virginia	1474.2	725.4	748.8	431.3	317.5
North Carolina	1518.2	603.2	915.0	490.1	424.9
South Carolina	1816.1	708.6	1107.5	616.8	490.7
Georgia	1607.3	702.2	905.1	490.1	415.0
Florida	1611.2	725.3	885.9	568.4	317.5
EAST SOUTH CENTRAL					
Kentucky	1394.8	673.3	721.5	381.0	340.5
Tennessee	1415.6	669.7	745.9	392.5	353.4
Alabama	1464.8	682.6	782.2	433.4	348.8
Mississippi	1455.6	680.0	775.6	437.2	338.4
WEST SOUTH CENTRAL					
Arkansas	1292.2	614.3	677.9	386.6	291.3
Louisiana	1681.8	751.7	930.1	595.2	334.9
Oklahoma	1336.2	632.8	703.4	433.8	269.6
Texas	1455.0	690.8	764.2	467.7	296.5

TABLE I. AVERAGE ANNUAL DEATH RATES PER 100,000 POPULATION FOR SELECTED CAUSES, WHITE MALES, AGES 45 TO 64, AGE ADJUSTED, BY STATE, 1949 TO 1951*—(CONT'D)

GEOGRAPHIC DIVISION AND STATE	ALL CAUSES	ALL CAUSES EXCEPT CARDIO-VASCULAR	DISEASES OF CARDIOVASCULAR SYSTEM (INTERNAT. LIST NO. 330-334, 400-468)		
			TOTAL CARDIO-VASCULAR DISEASES	CORONARY HEART DISEASE†	ALL OTHER CARDIO-VASCULAR DISEASES
MOUNTAIN					
Montana	1540.3	756.0	784.3	468.6	315.7
Idaho	1397.4	663.9	733.5	459.4	274.1
Wyoming	1370.0	705.3	664.7	427.2	237.5
Colorado	1369.9	699.7	670.2	439.1	231.1
New Mexico	1358.7	795.3	563.4	316.3	247.1
Arizona	1842.9	1063.7	779.2	435.1	344.1
Utah	1385.2	673.3	711.9	440.0	271.9
Nevada	1956.3	1015.6	940.7	576.0	364.7
PACIFIC					
Washington	1490.9	677.0	813.9	525.7	288.2
Oregon	1415.4	659.5	755.9	500.2	255.7
California	1685.1	780.1	905.0	621.2	283.8

Source: National Office of Vital Statistics[13] and Bureau of the Census.[14]

*Age adjusted by direct method to United States total population ages 45 to 64, 1950, by 5-year age periods. All rates by state of residence of decedent.

†Category 420 in International List of Diseases and Causes of Death, "Arteriosclerotic heart disease, including coronary disease."

coronary heart disease deaths and that there were no deaths whatsoever from cerebrovascular, rheumatic, or other forms of cardiovascular disease, the North Dakota rate is lower than the New York rate for coronary heart disease alone. This would seem to indicate that there is some difference in the rates for the two states, even though it may not be exactly of the magnitude indicated in Table I.

If the assumption is made that geographic differences in cardiovascular or coronary heart disease death rates are due to variations in judgments of physicians, then a negative correlation between cardiovascular and noncardiovascular and between coronary and other cardiovascular disease death rates would be anticipated. Actually, however, there is a positive correlation between death rates for cardiovascular disease and noncardiovascular disease ($r = + .44$), and between coronary heart disease and the other cardiovascular diseases ($r = + .34$). These correlations are both significant in a statistical sense at the 0.05 level. If for a given set of manifestations physicians extensively ascribed a death to one cause in one state and to something else in another, these geographic correlations would probably not be observed. The fact that such positive correlations exist (even though they are admittedly low) is in itself an interesting phenomenon suggesting that there may be agents affecting over-all death rates in the United States which are not cause specific, at least within the framework of present cause-of-death classification procedures. It is possible that part of

the real geographic variations in death rates for cardiovascular diseases or for coronary heart disease are due to such agents and that geographic patterns in these death rates will be understood only when they are identified.

CORRELATIONS WITH INDICES OF MEDICAL CARE

Where the ratio of internists to population is high, death rates for coronary heart disease are also high.[3] This is shown in Table II, along with ratios of physicians to population and an index of the completeness with which death certificates are filed—the proportion of death certificates filed with two or more causes of death listed. As can be seen in Table III, there is a high correlation between each of these indices and the coronary heart disease death rate.

All causes of death combined, however, also correlate highly with internists ($r = +.88$) and with physicians ($r = +.77$) (both significant at the 0.05 level), as well as with the completeness of death certificates ($r = +.53$). It could not be easily argued that increases in the quality and quantity of medical care cause increases in the total death rate. It seems more probable that such influences as urbanization and economic factors may be responsible for high death rates and may also cause large numbers of well-qualified physicians to locate in an area.

Since it seems illogical to assume that increasing the quality and quantity of medical care increases the total death rate, another approach seems needed for determining whether geographic variations in the quantity and quality of

TABLE II. SELECTED MORTALITY RATES AND INDICES OF MEDICAL CARE, BY GEOGRAPHIC DIVISIONS, UNITED STATES

GEOGRAPHIC DIVISION OF STATES*	DEATH RATES PER 1,000 WHITE MALES, AGES 45 TO 64, 1949 TO 1951†			INDICES OF MEDICAL CARE, 1950		
	ALL CAUSES	CARDIOVASCULAR DISEASES	CORONARY HEART DISEASE	INTERNISTS PER 100,000 WHITE POPULATION‡	PHYSICIANS PER 100,000 TOTAL POPULATION‡	PER CENT OF DEATH CERTIFICATES (ALL CAUSES) HAVING MORE THAN ONE CAUSE LISTED§
Middle Atlantic	17.2	9.3	6.2	12.6	168	64.0
New England	16.3	9.0	5.9	10.5	163	67.0
Pacific	16.3	8.8	5.9	9.7	147	63.5
East North Central	15.9	8.7	5.4	7.3	124	62.2
South Atlantic	15.8	8.9	5.2	8.8	104	56.1
West South Central	14.2	7.5	4.6	5.8	99	52.0
West North Central	13.4	7.2	4.5	6.7	119	64.0
Mountain	14.9	7.2	4.4	6.5	116	58.0
East South Central	14.1	7.4	4.0	4.5	81	47.4

*Arrayed by death rates for coronary heart disease (International List Cause 420).

†Computed from 1949-1951 average annual mortality[13] and 1950 population.[14]

‡Computed from number of internists (including cardiologists) and physicians in 1950[17] and 1950 population.[14]

§Estimated by the authors from a 10 per cent sample of death certificates filed in the National Office of Vital Statistics during the month of February, 1950. The following states are not represented: Massachusetts, Rhode Island, Wyoming, and Nevada.

TABLE III. COEFFICIENTS OF CORRELATION (PEARSONIAN r) OF DEATH RATES AND PROPORTIONATE MORTALITY WITH INDICES OF MEDICAL CARE, WHITE MALES, AGES 45 TO 64, UNITED STATES

CORRELATES	CORRELATION WITH INDICES OF MEDICAL CARE		
	INTERNISTS PER 100,000 WHITE POPULATION	PHYSICIANS PER 100,000 POPULATION	PER CENT OF DEATH CERTIFICATES (ALL CAUSES) HAVING MORE THAN ONE CAUSE LISTED
By 9 Geographic Divisions of States			
Death rates			
Cardiovascular diseases	+.86	+.70	+.54
Coronary heart disease	+.94	+.89	+.74
Cardiovascular diseases exclusive of coronary heart disease	+.05	−.27	−.34
Noncardiovascular causes	+.64	+.65	+.37
All causes	+.88	+.77	+.53
By 48 States			
Death rates			
Cardiovascular diseases	+.44	+.33	—
Coronary heart disease	+.57	+.60	—
All causes	+.45	+.36	—
Proportionate mortality			
Of total deaths, proportion due to cardiovascular diseases	+.12	+.07	—
Of total deaths, proportion due to coronary heart disease	+.37	+.54	—

Sources: Tables I and II and references 13, 14, and 17.

medical care constitute an important factor in cause-specific death rates. One possible approach involves the use of proportionate mortality. If physicians in one state are more prone to enter a cardiovascular cause on death certificates than physicians in another state, then a higher percentage of deaths would be ascribed to this cause in one state than in another. As is shown in Table III, the proportion of total deaths due to coronary heart disease is correlated moderately with the availability of internists and physicians ($r = +.37$ and $+.54$, respectively, both significant at the 0.01 level).

There is also a high correlation by states of mortality rates for all causes with rates for cardiovascular diseases ($r = +.87$) and for coronary heart disease ($r = +.77$). The coefficient of determination (r^2), 0.76 and 0.59, respectively, is the proportion of the variation in the specific causes which can be statistically explained by all causes. The residual variations (24 per cent for cardiovascular diseases and 41 per cent for coronary heart disease) are due to variations in proportionate mortality.

The coefficient of determination for internists and coronary heart disease proportionate mortality is 0.14, indicating that 14 per cent of the variation in proportionate mortality for coronary heart disease is statistically associated with the supply of internists; since 41 per cent of the variation in coronary heart disease rates is due to variations in proportionate mortality, then the product of these percentages, or 6 per cent of coronary heart disease rate variations, may be said to be statistically associated with the supply of internists in a way that might be causal. The same method of calculation indicates that 12 per cent of this variation is similarly associated with the supply of physicians.

The District of Columbia is excluded from these correlations, because the internists (and physicians in general) serve a substantial population living outside its boundaries and because there is no way readily apparent for estimating this population satisfactorily. The internists (and physicians in general) in some of the states likewise serve a population either greater or smaller than the population of their state, because people may go to any nearby city for medical care without regard to state boundaries. A careful inspection of scatter diagrams, however, shows clearly that to make an allowance for the populations actually served would make no appreciable change in the correlations.

Similar calculations indicate that not more than 5 per cent of the variations in cardiovascular disease death rates are statistically associated (in a way that might be causal) with the availability of either physicians or internists. The results are essentially the same whether the correlations are made for 48 states or for 9 geographic divisions of states.

It seems reasonable to assume that there will be differences geographically in the proportion of total deaths due to cardiovascular diseases, if for no other reason than that the death rates for specific causes such as auto accidents and tuberculosis vary. If the same factors which cause large numbers of well-qualified physicians to locate in an area are responsible for high death rates for all causes, possibly they are responsible to some extent for the high proportionate mortality for cardiovascular and coronary heart disease as well.

In any event one might expect a high physician-population ratio to have a more favorable effect on decreasing the noncardiovascular diseases than the cardiovascular diseases (in view of greater therapeutic advances for noncardiovascular diseases evidenced by greater declines in death rates for noncardiovascular as compared with the cardiovascular diseases during the past few years), and thus increase proportionate mortality. Thus, only a nominal proportion of the geographic variation in death rates for cardiovascular diseases appears at present to be due to the variations in the judgments of physicians signing death certificates, and not more than a small portion, possibly less than one-tenth, of the variation in coronary heart disease death rates is similarly caused.

THE ACCURACY OF POPULATION AND TOTAL DEATH COUNTS

It is, of course, possible that some of the geographic variation in the death rate for all causes results from a combination of inaccuracies in population and total death counts. This would cause geographic variations in death rates for

cardiovascular and coronary heart disease, as well as for all causes, to be observed when they did not truly exist. The available evidence indicates that while there are some such inaccuracies, they are probably too small to have much effect on the death rate. The Bureau of the Census estimates that in 1950 the net underenumeration was "at least 1.4 per cent."[14] The enumeration of white males aged 45 to 64 is probably more nearly complete than that for the population as a whole according to Coale's[18] estimate. Underenumeration of the total population is greatest in the South (1.8 per cent) and least in the Northeast (0.8 per cent). Thus the differences in underenumeration among geographic areas are fairly small. Moreover, any correction for such underenumeration would tend to increase rather than decrease the differences in death rates shown in Table I.

Nor is there reason at present to believe that for whites important differences exist among the states in the completeness with which death certificates are filed. The birth registration check conducted in 1950 revealed that birth registration for whites is roughly 99 per cent complete and it is believed that death registration is somewhat more complete than birth registration.[13] We might, therefore, conclude that death rates for all causes are fairly accurate when tabulated by states.

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CAUSE OF DEATH CHECKED BY AUTOPSY

There can be little doubt that death rates are questionable for certain relatively small subgroups to which deaths are coded. In a study by James, Patton, and Heslin,[5] for example, it was found that the number of deaths classified as due to hypertension with heart disease (codes 440-443) was decreased by 51 per cent when autopsies were done, a reflection of a substantial difference in medical opinion. On the other hand, the same study has shown that of 276 deaths classified as due to coronary heart disease, 75 were found on autopsy to be due to other causes; but 66 ascribed to other causes based on clinical examination were classified on autopsy as due to coronary heart disease. Thus there was a corrected total of 267 coronary heart disease deaths, a decrease from the original figure of only 3.3 per cent. No other studies have been located for similar comparison of agreement in classification of coronary heart disease.

A somewhat smaller net change was observed for those deaths classified as cardiovascular or cardiovascular-renal, as is shown in Table IV. Table IV also summarizes all other available studies in which data were presented in a way to obtain a total for either cardiovascular or cardiovascular-renal mortality, both before and after correction.

All studies revealed rather small net errors, ranging from 1 to 7 per cent. While these six studies lack geographic representation for specific application to a study of mortality variations by states, they do provide some assurance that, for the disease categories considered here, death rates in general are reasonably accurate. Moreover, it has been suggested that hospital autopsy studies, upon which most of the data summarized in Table IV were based, may show a greater percentage error than exists for all deaths because such studies include cases presenting special problems in differential diagnosis.[24]

TABLE IV. ADJUSTMENTS IN NUMBER OF CARDIOVASCULAR DISEASE DEATHS RESULTING FROM PATHOLOGIC AND OTHER SPECIAL STUDIES FOR AREAS WITH DATA AVAILABLE

AREA AND GROUP IN STUDY	YEAR	AUTHOR	SOURCE OF DATA FOR ADJUSTMENT	TOTAL DEATHS IN STUDY	CARDIOVASCULAR DISEASE DEATHS*			CARDIOVASCULAR-RENAL DISEASE DEATHS		
					ORIGINAL DIAGNOSES	DIAGNOSES RESULTING FROM STUDY	PER CENT CHANGE AS A RESULT OF STUDY	ORIGINAL DIAGNOSES	DIAGNOSES RESULTING FROM STUDY	PER CENT CHANGE AS A RESULT OF STUDY
Albany, N. Y., region, 12 hospitals	1951-52	James, Patton, and Heslin[5]	Autopsy	1,889	599	590	—1.5	622	616	—1.0
England and Wales, death certificates with "ill-defined" (or inadequately defined) causes	1950	World Health Organization[19]	Query to physician	12,391†	3,233	3,461	+7.1	3,527	3,679	+4.3
New York City proprietary hospitals	1937-1939, 1941	Jacobson[6]	Hospital charts, records	7,330	NA‡	NA	NA	1,954	1,883	—3.6
New York and New Jersey cities, 15 hospitals	1930-1939	Pohlen and Emerson[20-22]	Autopsy	25,066	4,544	4,410	—3.0§	4,934	4,782	—3.1
Los Angeles County, Calif., General Hospital	1933-1937	Swartout and Webster[23]	Autopsy	8,080	1,473 ‖	1,359 ‖	—7.7	NA	NA	NA
Magdeburg, Germany	1928-1936	Pohlen[22]	Autopsy	8,182	1,489	1,417	—4.8	1,589	1,535	—3.4

*Sixth International List code numbers 330-334 and 400-468 or approximate equivalent in earlier lists.

†Queries made because of incompleteness or lack of consistency or clarity in entries on death certificate.

‡Not available.

§Including "arteriosclerotic kidney" which is included in the Sixth International List of Causes of Death (1948) as part of cardiovascular diseases. When excluded, original diagnoses of cardiovascular total 3,953, corrected diagnoses 3,005, a reduction of 24.0 per cent, but the authors[20] explain that this is primarily a problem in classification.

‖ Diseases of the heart and cerebral hemorrhage.

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SUMMARY

No doubt the assignment of causes of death is often inaccurate, and any practicing physician can probably recall a large number of instances in which the cause of death was improperly entered on the death certificate. The magnitude of such inaccuracies undoubtedly varies somewhat from state to state and these inaccuracies may very well account entirely for small differences in death rates for cardiovascular diseases or coronary heart disease.

It seems unlikely, however, that they could account for all of the large differences in death rates shown here. Evidence presented may be summarized as follows:

1. The contrasts in death rates for cardiovascular diseases for some states, such as South Carolina and North Dakota, are sufficiently great to make it seem certain that some real differences exist. It seems likely that real geographic variations in death rates for cardiovascular disease and coronary heart disease of considerable magnitude exist within the United States.

2. The quality and quantity of physicians available do not appear to have an appreciable effect upon cardiovascular death rates, and only a small percentage of the variation in coronary heart disease death rates appears to be related to this factor.

3. Population and total death counts appear to be fairly accurate.

4. Autopsies and other studies indicate that, in general, errors in cause-of-death entries on death certificates tend to be compensatory, so that for major groupings such as cardiovascular diseases or coronary heart disease net errors in the counts are possibly less than 7 per cent.

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WORK EXPERIENCE OF PERSONS WITH CARDIOVASCULAR DISEASE OR DIABETES

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DISEASES of the heart constitute one of the most important individual and public health problems in the United States today. It is estimated that there are at least ten million Americans, or between 5 and 6 per cent of our total population, with some form of heart disease.[1] According to other studies, nearly 10 per cent of the population has cardiac disease; on the basis of this estimate, about seven million persons in the labor force are afflicted with heart disease.[2] It is also said that "if half of the survivors of coronary disease return to work, 400,000 to 500,000 persons are being added yearly to the labor market."[3] Thus, by virtue of its magnitude, the problem of heart disease should be of great concern not only to private practitioners, but also to industrial physicians.

Although there is almost universal agreement among private and industrial physicians that, under proper care and management, persons with cardiac disease can and should work,[5] a large proportion of persons with heart disease have difficulty finding employment, for it is still common practice in industry not to hire persons known to have cardiac disability. Barriers to employment appear to include such factors as: workmen's compensation liability, sickness insurance liability, low productivity, the existence of suitable jobs, absenteeism, and union seniority requirements.[4]

The primary purpose of this paper is to examine the role of the industrial medical department in the management of persons with cardiovascular disease and other disease. In essence, the *raison d'etre* of industrial medical departments

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This is part of a larger study which analyzes in detail various aspects of the work experience of persons with cardiovascular disease and of comparable controls, including absence experience, medical history, and records of visits to industrial medical departments and sick benefit compensation.

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is said to be the maintenance of employees' health and the reduction of absenteeism, injuries, and their sequelae. A recent study of managerial attitudes toward employee health services reports that managers and company medical staffs use lost-time rates as criteria for measuring the effectiveness of medical personnel.[6] While savings to industrial organizations realized by reduction of workmen's compensation claims have been measured directly, little has been done in the way of relating medical facilities to absence. In general, it would be expected that the more care and attention an individual receives from his company clinic, the better the chances for preserving his general health and well being and the lower his absenteeism will be.

We recognize that a multitude of factors influence absence experience, among which are health and personality characteristics, employee attitudes, supervision, salary, vacation, sick leave, other company policies and benefits as well as innumerable hidden factors, and that we are dealing with one facet of a complex problem. This study which is focused principally on absenteeism and clinic visits, therefore, is limited and the results presented are intended to be suggestive rather than definitive.

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PROCEDURE

Data for the study were obtained for 691 persons with cardiovascular disease or diabetes and 691 persons who were free from these diseases (selected to serve as a matched comparison or control group). The persons included were employees of 17 firms in the Greater Boston and New York areas, western Massachusetts, and Connecticut. The industries participating in the study varied considerably in type of industry, size (number of employees), composition of the labor force, personnel policies, and company benefits, and in other respects. The characteristics common to all were the presence of well-established medical departments under the direction of either full- or part-time physicians and a policy to keep employed as many persons as possible who develop cardiac disability and, in addition, the practice of some organizations to hire persons with known cardiac disease and diabetes.

In many companies, employees with cardiovascular disease or diabetes were identified by company personnel. With this as a starting point, selection of cases for the study was made on the basis of a careful examination of company medical records by the physician on the project staff to ensure that the medical criteria for cardiac and related diseases, as defined for purposes of this study, were complied with. In this study, diagnosis for heart disease conforms to the American Heart Association's Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Blood Vessels. In addition to a review of existing company records, in selected cases, physical examinations were conducted to determine cardiovascular and diabetic status, and in other cases, hospital records and records of private physicians were examined.

The controls used in the study were employees matched on a one-to-one basis with persons having cardiovascular disease; matching, insofar as possible, was done with respect to age, sex, occupation, department, length of service, and

marital status. The medical records of these employees were also carefully examined by a staff physician to ensure that there was no evidence of cardiovascular disease or diabetes. Where records did not contain sufficient information for ruling out these diseases, the individual was not included in the study.

DESCRIPTION OF SAMPLE

The diagnostic classification of the 691 persons with cardiovascular and related disease is shown in Table I. The 691 controls were classified as shown in Table II.

The number of employees chosen from each of the 17 firms studied varied from 8 to 200 with the median about 66. Represented in the study were two

TABLE I. DIAGNOSTIC CLASSIFICATION OF 691 PERSONS WITH CARDIOVASCULAR DISEASE OR DIABETES

PRIMARY DIAGNOSIS	NUMBER OF PERSONS
Coronary heart disease	291
Rheumatic heart disease	63
Hypertensive heart disease	95
Other heart disease	38
Hypertension (systolic 180+, diastolic 100+)	148
Diabetes mellitus	56
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TABLE II. CLASSIFICATION OF 691 PERSONS IN CONTROL GROUP

CONTROLS	NUMBER OF PERSONS
Borderline hypertension (systolic 150 to 180, diastolic 90 to 100)	212
Normal blood pressure (systolic <150, diastolic <90)	479
	691

hospitals, an insurance company, light industries such as instrument manufacturers and a publishing house, heavy industries such as shipbuilding and aircraft manufacturers. The total size of companies ranged from 750 to 40,000 employees. The median age for the selected sample was about 55 years and only about one-sixth of the group were under 45. Four-fifths were men, most of whom were married. Of the women, about one-half were married; the rest were single, widowed, or divorced. About one-half of the sample were in production positions such as skilled, semi-skilled, and unskilled; about one-fourth were in professional and managerial positions, one-sixth in clerical positions, and the rest in service positions, including guards, janitors, matrons, etc. Occupational classification was made according to the *Dictionary of Occupational Titles of the Bureau of Labor*

Statistics. About one-half of the persons studied had 15 years of service with their company and only 1 in 8 had less than 5 years. The great majority were American born. Educational experience ranged from grammar school to the Ph.D. level.

FINDINGS

Absence experience and clinic visit experience for the period of one year were studied. For purposes of this study, the major measure of absence was the disability rate or the number of days of absence per 100 scheduled work days,* (also called the lost-time rate or the per cent of lost work time). Clinic visit experience was studied by analysis of all visits to the company medical department, the reasons for the visit, the number of visits made per condition, and whether the visit was related to absence.

Absence Experience.—Before relating the effects of medical management by the industrial physician to the work performance of the employee with cardiovascular disease and diabetes, it may be well to provide a base line by comparing the work experience of persons with cardiac and related disease with that of matched controls.

In the sample studied, persons with cardiovascular disease and diabetes lost more work time for all reasons than did a comparable group of persons who were free from these diseases. The disability rates were 5.9 and 3.3, respectively; in terms of work days lost per year, the study group (cardiovascular and diabetes group) lost an average of 13.7 work days, the matched control group 7.6 work days. Although the difference in rates is not likely to be due to chance, (i.e., is statistically significant), its magnitude is not great, amounting to an average loss of 6.1 more work days per year for persons with cardiovascular and other disease than for those free from these diseases. Perhaps of greater interest is the fact that nearly one-half of the study group lost less than 5 work days for all reasons and that over two-fifths lost no time because of nonoccupational illness. Thus, the findings of this study support the views of many private and industrial physicians that cardiac and diabetic patients can work in competitive industry.

Of interest, too, are the findings that there are great variations in the disability rates of the groups from each of the participating firms, (Fig. 1). For the study groups, the range in disability rates was from 1.04 to 11.80 with the median 6.90; for the matched control groups, the variability, though less great, was nevertheless marked—from 1.29 to 7.05—with the median 3.06. In only two companies were the rates for the control group higher than those for the study group. Further, among study persons, 13 of the 17 company groups had disability rates of 4.00 or more; among controls, only 4 of the 17 company groups had disability rates this high or higher. Much of the difference among the company groups is likely to be due to differences in the composition of the groups in terms of such factors as the type of cardiovascular disease most prevalent, the age,

*An absence was defined as time away from work for more than 4 continuous hours. Scheduled work time included the regular 5 or 6-day week, but excluded time away from the job because of vacation, holidays, jury duty, military duty, layoffs, and strikes.

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sex, occupational, and length of service distributions, as well as working conditions and company benefits within the company groups. However, the data seem to indicate that regardless of the effects of these variables persons with cardiovascular disease or diabetes are likely to lose more time than persons free from such diseases, though the difference is not necessarily large.

It may be seen that age group by age group, persons with cardiovascular disease and diabetes lost more time than did the controls (Table III). Of especial significance to persons concerned with employment for older persons is the finding

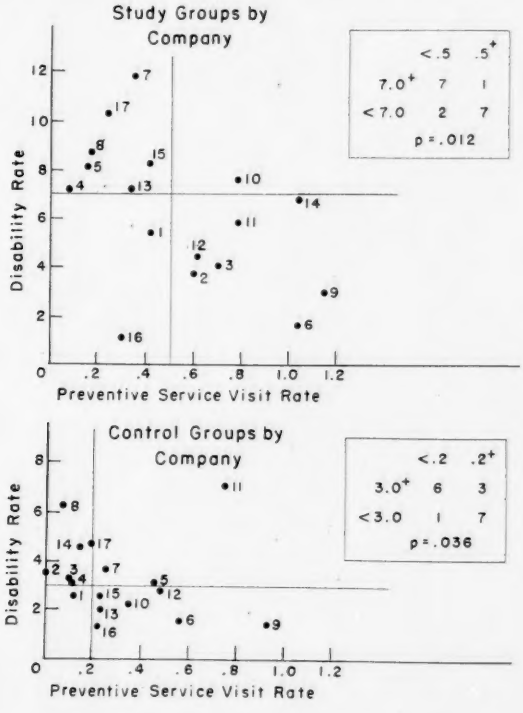

Fig. 1.—Disability rates and preventive service visit rates (one year's experience). *1*, Wire and Cable. *2*, Hospital A. *3*, Life Insurance. *4*, Greeting Card. *5*, Engine Manufacturers. *6*, Soap and Soap Products. *7*, Instrument Manufacturers. *8*, Shipbuilding. *9*, Utility Company. *10*, Petroleum Refinery. *11*, Hospital B. *12*, Aircraft Engine. *13*, Service Station Equipment. *14*, Airplane Manufacturers. *15*, Paper Products. *16*, Steel Machinery. *17*, Rubber Products. Note: The median test and the Fisher Exact Probability Test were used to test for association (see Siegel, S.: Nonparametric Statistics for the Behavioral Sciences, New York, 1956, McGraw-Hill Book Co., Inc.).

that, among persons with cardiovascular and other disease and among controls, persons under 45 had higher lost-time rates than did older persons. The results of this study thus support the findings of other investigators who report that in terms of absenteeism, older workers compare favorably with their younger counterparts.[7] The relatively high rate for study persons under 45 may be accounted for by the high proportion of persons with rheumatic heart disease found in this

TABLE III. DISABILITY RATES BY NUMBER OF CLINIC VISITS FOR PREVENTIVE SERVICES
(One Year's Experience Study and Control Groups Compared)

NUMBER OF VISITS	STUDY GROUP			CONTROL GROUP		
	CASES		DISABILITY RATES	CASES		DISABILITY RATES
0	301		6.3	440		3.7
1	173		5.1	150		2.9
2–3	155		5.9	76		2.1
4–5	37	217	7.1	18	251	2.4
6–9	19		6.5	5		
10+	6		3.2	2		1.3
All	691		5.9	691		3.3

DISABILITY RATES FOR INDIVIDUAL CATEGORIES

SEX

	MALES	FEMALES	MALES	FEMALES
0	6.2	5.6	3.6	4.0
1	5.1	5.2	2.5	4.1
2+	6.4	4.4		
All	6.0	5.3	3.1	4.0

AGE

	<45	45–54	55+	<45	45–54	55+
0	7.8	4.6	6.8	4.0	3.8	3.4
1	4.4	4.6	5.8	3.9	2.7	2.3
2+	6.8	4.9	6.5			
All	7.0	4.7	6.4	4.0	3.3	3.0

age group. Of all the cardiac groups, those with rheumatic heart disease lost the most time. The findings also show that many persons with heart disease, particularly coronary heart disease, are able to work with little more disability than persons free from heart disease; at ages 45 to 54, the differences in absenteeism between study persons and controls amounted to only about 3 work days per year. At age 55 and beyond, there seems to be a decrease in functional ability of study persons which is reflected in increased absence from work.

By sex, both men and women study persons had higher lost-time rates than did the matched controls. In the study group, women had lower rates than men, a result accounted for in part by the fact that a large proportion of the women studied were hypertensives without evidence of cardiac involvement. Some investigators report that in general women lose about twice as much time from work as men, but in this study the rates for the control group show considerably

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TABLE III. DISABILITY RATES BY NUMBER OF CLINIC VISITS FOR PREVENTIVE SERVICES (One Year's Experience Study and Control Groups Compared)—Cont'd

VISITS	STUDY GROUP				CONTROL GROUP			
DISABILITY RATES FOR INDIVIDUAL CATEGORIES—CONT'D								
OCCUPATION								
	PSM	CLER.	SERV.	PROD.	PSM	CLER.	SERV.	PROD.
0	5.0	4.9	4.4	7.4	2.5	3.4	4.8	4.0
1	4.0	4.9	4.4	5.8	1.3	4.4	3.6	3.0
2+	3.0	5.7	3.7	9.6				
All	3.8	5.1	4.2	7.5	1.9	3.6	4.4	3.6
LENGTH OF SERVICE (YEARS)								
	<10	10–19	20+		<10	10–19	20+	
0	7.1	5.2	6.5		4.7	3.1	2.8	
1	4.9	6.0	4.5		4.7	2.5	1.6	
2+	5.2	9.7	5.3					
All	6.0	6.3	5.6		4.7	2.9	2.2	
DIAGNOSIS								
	ASHD	OTHER H.D.	HBP	DM	NORMAL	BHBP		
0	7.0	6.6	5.8	3.6	3.6	3.8		
1	4.9	6.8	3.3	5.8	2.5	2.9		
2+	6.6	5.6	5.2	6.0				
All	6.3	6.4	5.0	4.6	3.2	3.5		

PSM = Professional, semiprofessional, and managerial employees.
Cler. = Clerical.
Serv. = Service.
Prod. = Skilled, semiskilled, and unskilled employees.
ASHD = Coronary heart disease.
Other H.D. = Rheumatic heart disease, hypertensive heart disease, and other heart disease.
HBP = Hypertension.
DM = Diabetes mellitus.
BHBP = Borderline hypertension.

less difference between men and women. However, when the marital status of women was taken into account, the rates for married women were found to be higher than those for single and widowed women and considerably higher than the rates for married men. That employment is often a secondary responsibility for married women is thus reflected in their work experience.

By occupation, for each of the groups considered, except service personnel such as janitors, guards, etc., rates were higher for persons with cardiac and related diseases. Among study persons and the controls, persons in professional, semiprofessional, and managerial positions all tended to lose less time from work

than persons in other occupations; production workers—skilled, semiskilled, and unskilled—tended to lose the most time. Moreover, in both relative and absolute terms, the difference between the rates of study persons in production positions and controls in similar positions was greater than that for persons in other occupations. While the finding that persons with cardiac disease doing more physically strenuous work, i.e., production work, have more disability (as reflected in absence from work) than persons in lighter positions is contrary to the findings of Morris and his associates,[8] it supports the views of many physicians in American industry who report the desirability of careful placement of persons with heart disease.

By diagnosis, persons with heart disease lost more time from work than those with hypertension and diabetes. Employees with rheumatic heart disease as the primary diagnosis lost the most time; their disability rate was 9.2; next were those with coronary heart disease as the primary diagnosis, 6.3; followed by hypertensive heart disease, 5.6, and other heart disease, 4.9.

Clinic Visit Experience.—The question now arises as to the responsibilities assumed by industrial medical departments for the clinical management of employees with cardiovascular disease. As mentioned at the outset, all of the participating firms have established medical departments under the direction of physicians and all are aware of the cardiac problem in industry. They do, however, differ in their medical policies, the number of medical personnel, their physical facilities and equipment, and the scope of their functions and programs. For example, while all the participating medical departments give pre-employment or preplacement physical examinations, annual periodic examinations are offered by only a few. Some departments have highly refined methods for selective placement and matching abilities to job demands for all employees; others only follow up persons with selected disabilities by means of medical check-up; and in still others, periodic medical examinations are the exception rather than the rule. All of the medical departments in the study treat occupational accidents and give at least emergency treatment for nonoccupational illness and accidents. In some, visits to the medical department following all sickness absence are required; in others, visits to the clinic are entirely voluntary and are up to the individual employee. In addition to explicit policy regarding the use of medical department facilities, other factors such as general company policy, foremen's or supervisors' attitudes toward visits to the clinic, accessibility of the clinic, type of work performed (e.g., risk of accidents), the composition of the work force, and other factors are also important.

Considerable variation was found in the clinic visit rates (number of clinic visits per 100 scheduled work days) of the employees of the participating companies reflecting the influence of the factors cited above (Table IV). For example, rates for occupational accidents are low in the life insurance company, utility company, and hospitals A and B, in comparison with rates for other companies, but the differences may be accounted for in large part by the fact that the groups studied from these companies are mainly in nonproduction positions.

With respect to preventive service visits, rates are high for the utility company, soap and soap products manufacturers, and airplane manufacturers.

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At the utility company, the groups studied are entirely composed of executive and mangerial personnel; further, in part because of the research interests of the medical director, periodic examinations are given on a voluntary basis semiannually. Similarly, at the soap and soap products manufacturers, the group is eligible for annual periodic examinations. Employees of the airplane manufacturers with cardiovascular disease or diabetes are singled out for special medical follow-up by means of annual and semiannual examinations; persons free from these diseases (the matched control group) except for those in special job categories, do not receive periodic examinations. (Note the difference in rates between the study and control groups—1.03 *vs.* 0.14).

TABLE IV. CLINIC VISIT RATES, BY REASON FOR VISIT AND BY COMPANY (One Year's Experience Study and Control Groups Compared)

COMPANY	RATES (VISITS PER TOTAL SCHEDULED WORK DAYS × 100)							
	ALL REASONS*		NONOCCUPATIONAL ILLNESS		OCCUPATIONAL ACCIDENTS		PREVENTIVE SERVICES	
	STUDY	CONTROL	STUDY	CONTROL	STUDY	CONTROL	STUDY	CONTROL
Wire and Cable	4.90	6.27	2.77	2.15	0.92	3.49	0.42	0.12
Hospital A	1.83	1.68	0.80	1.48	0.35	0.13	0.60	0.00
Life Insurance	5.09	2.86	3.18	1.39	0.19	0.09	0.71	0.09
Greeting Card	2.33	1.43	0.51	0.64	1.22	0.41	0.08	0.10
Engine Manufacturers	0.78	1.20	0.24	0.19	0.36	0.49	0.16	0.47
Soap and Soap Products	5.74	2.46	4.48	1.69	0.14	0.18	1.05	0.56
Instrument Manufacturers	4.07	1.77	1.89	0.59	1.27	0.56	0.34	0.25
Shipbuilding	1.29	1.23	0.57	0.57	0.46	0.52	0.17	0.07
Utility Company	2.96	2.70	1.72	1.38	0.01	0.00	1.15	0.93
Petroleum Refinery	4.98	1.86	2.74	1.02	1.18	0.42	0.78	0.35
Hospital B	3.08	2.00	1.86	1.07	0.14	0.09	0.79	0.74
Aircraft Engine	2.65	2.90	0.63	0.46	1.02	1.78	0.62	0.48
Service Station Equipment	3.75	4.82	2.15	1.82	0.80	2.57	0.35	0.23
Airplane Manufacturers	2.95	1.82	1.16	0.65	0.67	0.90	1.03	0.14
Paper Products	6.37	5.11	5.39	3.59	0.44	1.01	0.41	0.23
Steel Machinery	0.63	1.55	0.10	0.93	0.21	0.41	0.31	0.21
Rubber Products	3.74	3.42	1.84	1.53	1.07	1.06	0.24	0.18
Total	3.29	2.65	1.73	1.10	0.59	0.88	0.60	0.30

*Includes visits for occupational illness and nonoccupational accidents.

Rates for visits for nonoccupational illness also display a wide range by company. At the engine manufacturers and shipbuilding company, visits for the treatment of minor ailments, such as headaches, minor colds, and sore throats, etc., are not encouraged and rates of visits are low; on the other hand, at the paper products and wire and cable companies, the atmosphere of the clinic is permissive and employees are encouraged to make visits whenever they like. Personnel of the petroleum refinery and service station equipment company are required to make visits to the medical department following each sickness absence.

Absenteeism and Clinic Visits.—Having described briefly absence experience and clinic visit experience among a sample of employees with cardiovascular disease and diabetes and of persons free from these diseases, we may now study the role of the industrial medical department in the management of such persons on a quantitative basis. In general, it would be expected that the more effective medical care an individual receives, the better his health will be. By relating measures of medical care and health which are available for this study—visits to industrial medical departments and time lost from work—this hypothesis may be tested. Rates of clinic visits for all reasons and disability rates were correlated by means of scatter diagrams (not shown). It was found that among persons free from cardiovascular disease and diabetes (controls) low lost-time rates were associated with high rates of clinic visits for all reasons. Among persons with cardiovascular disease and diabetes, this relation was not found. Since some clinic visits are return-to-work visits following absences, and since persons with cardiovascular disease and diabetes had relatively high lost-time rates, the finding of no relation between clinic visits and lost time is not surprising.

It was found, however, that low lost-time rates are associated with high clinic visit rates for nondisabling nonoccupational illness. Among control groups by company, the correlation was statistically significant; among study groups, the relation was in the direction expected, but the results were not statistically significant (scatter diagram not shown).

Most striking and of greatest importance are the results shown in the graphs correlating preventive service rates and disability rates (Fig. 1). For both study and control groups by company, absenteeism was significantly lower among those with high rates for preventive service visits; ($P = 0.012$ for study groups; $P = 0.036$ for control groups). By definition, for this study, preventive services include periodic examinations, some of which are comprehensive and include a complete battery of laboratory and diagnostic procedures; brief follow-up such as blood pressure check-up, roentgenograms, electrocardiograms, etc.; evaluation of functional capacity and selective job placement; vaccinations and other immunizations; eye refractions; health education and personal counselling and the like. In many cases, periodic physical examinations result in the detection of disease not previously known. Employees are often advised about the treatment to be sought in controlling the conditions discovered and are followed at varying intervals to determine whether the necessary treatments have been obtained.

While the data reported here do not take into account such qualitative factors as the kind of service rendered, e.g., whether the visit was for the purpose of a periodic physical examination, a blood pressure check, etc., the relative importance of the service as a preventive measure, nor other important factors such as employee attitudes, general working conditions and company policies and benefits; the findings certainly have major implications for industrial physicians. The data also suggest a point of departure for more detailed and intensive study of the relation between medical management and disability.

Further analysis of the data supports the finding that preventive service visits are negatively associated with lost-time rates. About 44 per cent of the

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study group made no visits for preventive services during the year under study, 25 per cent made only one visit, and 30 per cent made two or more visits. Sixty-four per cent of the matched control group made no visits for preventive services, 22 per cent made one, and 14 per cent made two or more. The disability rates for the cardiovascular and diabetes groups were: 6.3, 5.1, and 6.1; for the control groups: 3.7, 2.9, and 2.2 (Table III). It is noteworthy that a nonlinear trend in the lost-time rates of the study groups was observed. It can be hypothesized that persons making one visit for preventive services, which was most likely a periodic physical examination, are made health conscious and therefore are likely to have sought medical treatment when and where indicated, to have modified their behavior in terms of their health status, and to be well placed on their jobs. In brief, some of the desirable preventive measures have been effected. On the other hand, persons with no record of preventive service visits are not likely to have had their health status evaluated recently. A limitation of the data should not be overlooked. The period under study was one year, and from the data in this study, there is unfortunately no way of knowing whether a periodic examination was given in the preceding year. Thus, the beneficial effects of preventive services on health are reflected in the disability rates. Still to be considered, however, is the group of study persons making two or more preventive service visits; their disability rate was higher than that of the group making one visit. It can be said that persons who require frequent preventive services usually come in for the check-up of known conditions. In most of the companies in the study, periodic examinations are given yearly or less often. Thus, for those making frequent visits, some of whom may have acute and disabling conditions, it is possible that optimum medical management has been effected and that little can be done to reduce their absenteeism further.

Analysis by personal and employment characteristics of the samples studied also points up the beneficial effects of preventive services on lost-time rates (Table III). With relatively few exceptions, it was found that, among persons with cardiovascular disease or diabetes, those making no preventive service visits tended to lose more time from work than those making one visit. In some cases, persons making two or more visits lost more time than those making one visit. Among the controls, persons making no preventive service visits tended to lose more time than those making one or more visits. The evidence from this study should certainly encourage industrial medical departments to expand their preventive programs.

SUMMARY AND CONCLUSIONS

This study reports the results of analysis of work experience of 691 persons with cardiovascular disease or diabetes and 691 matched controls from 17 different firms and institutions. It was found that employees with cardiovascular disease or diabetes can and do work although their attendance record is not quite as good as that of their counterparts. Those between 45 and 54 lost only slightly more time from work than did comparable controls; those under 45 and those 55 and over compared less favorably with their controls. Persons with rheumatic heart disease, most of whom were under 45, lost more time from work than

any of the other groups studied; the coronary heart disease group, the largest of the cardiac groups, had the next highest disability rate. Of major significance to industrial physicians is the finding that persons with cardiovascular disease or diabetes in nonproduction positions lose nearly as little time from work as their matched controls, but that production workers with these diseases lose significantly more time than their matched counterparts. The data suggest the desirability of systematic careful placement for employees with cardiovascular disease and diabetes.

All of the companies participating in the study have well-established medical departments under the direction of physicians, but they differ in size, facilities, policies, and scope of functions and services. The frequency of visits to the company clinics or medical departments (rates of clinic visits) varied considerably among the employee groups studied. The variation may be accounted for both by the composition of the employees studied as well as by company and medical department policies.

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Analyses of the relation between clinic visits and time lost from work show a negative relation between utilization of clinic facilities and absence from work. Most striking was the observation of a significant relation between preventive service visits and disability rates. Both for persons with cardiovascular disease and diabetes and for persons free from such diseases, it was found that medical care given by company medical departments in the form of preventive services was associated with lower disability rates. Of interest was the finding that among persons with cardiovascular disease or diabetes the association was not linear. In general, persons who made one preventive service visit during the year under study tended to lose less time from work than those making no preventive visits and than those making two or more preventive visits. The inference to be drawn from the findings may be that persons making frequent visits for check-ups are likely to be more seriously disabled than those not requiring intensive medical surveillance and attention. The nature of the disabilities of the former group may be such that little more can be done through the efforts of the company medical departments to reduce absenteeism further, and the severity of the conditions may be manifested in higher disability rates. Among those free from cardiovascular disease and diabetes, the trend was consistent—persons making one or more preventive visits lost less time from work than those making no preventive visits.

The problem of absenteeism is a complex and intricate one, and the results of this paper do not purport to be definitive. However, the findings indicate that persons with cardiac and diabetic diseases can and do work. Further, medical management by the industrial physician appears to have an important role in improving work performance, for it was found that absenteeism may be reduced through the efforts of industrial medical departments. Key factors in the reduction of disability and time loss from work seem to be preventive services such as: periodic physical examinations, selective job placement, follow-up and check-up, immunizations, health counselling, and education. Although the data in this study are limited and do not provide clear-cut definitive answers to the role of medical departments in health maintenance and disability limitation, neverthe-

less, they point to a need for intensive, qualitative study of the factors which influence absence experience and suggest that industrial medical departments could profitably increase and expand their medical programs emphasizing the broad principles of prevention.

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Book Reviews

EXPERIMENT PERILOUS. PHYSICIANS AND PATIENTS FACING THE UNKNOWN. By Renée C. Fox. Glencoe, Ill., 1959, The Free Press. Pp. 262, index. Price $5.00.

Miss Fox is a sociologist who spent many months observing doctor and patient behavior on a research metabolic ward at what appears to be the Peter Bent Brigham Hospital. The verbatim (? shorthand) transcript of what the doctors and patients said is the meat of the book. The remarks are touching, pathetic, inspiring, frightening, and macabre in turn. Unfortunately, as Miss Fox herself suspects (on p. 221), what the material cries for is a novelist's sure touch. The author's editors have also not helped her much; the book is repetitious and not infrequently pedantic. The author's interpretations seem to contribute little. On the other hand, any doctors who need reminding (and who doesn't?) of the problems facing the clinical investigator and his patients would find sections of this book fascinating.

Louis Lasagna

A HISTORY OF OPHTHALMOLOGY. By George E. Arrington, Jr., M.D. Foreword by Félix Martí-Ibáñez, M.D. New York, 1959, MD Publications Inc. Pp. 174, indexed. Price $4.00.

The good aspects of this book are represented in the documentation of ophthalmologic thought and progress over the centuries. The unfortunate fact is, however, that the author has also tried to write a philosophic, "holistic" (How that word is popular nowdays!) treatise. And Dr. Arrington is not quite up to this task. Despite the editor's statement that the author is "as distinguished a historian as he is an ophthalmologist," Arrington is, after all, a young man barely out of his residency training. The job he has set for himself has not been accomplished satisfactorily very often in medical history, and the current opus is (not surprisingly) superficial, half-baked, pompous, or puerile from time to time. Here are some samples:

"But the thinker of our day who remains shackled to materialism seems definitely to be defending a lost cause. The lesson of the downward trend of materialistic scientific thought teaches the need for flexibility but does not weaken belief in a possible final resolution of comprehensiveness through science, so far as human intelligence is able to proceed. The same lesson teaches us to beware of fixing our minds so statically within the confines of a narrow system of scientific thought that we fail to glimpse a new but, by this set of standards, a bizarre revelation of truth." (p. 93.)

"One is tempted to assign the decrease of this self-discipline in our day to general modern cultural trends in which more and more of our daily tasks are done by machines and industrial services. This weakens moral fiber and ingenuity . . . Small wonder that during an *electrical* power failure, ophthalmological practice all but ceases." (pp. 125-126.)

"History shows that the problems of visual disturbance touch the depths of human personality and demand attention from thinkers possessing equal profundity. History demands that the ophthalmologist who seeks to contribute originality *must study man before he studies man's eyes.*" (p. 81.)

In regard to the last quotation, it is indeed true that many great figures in medicine (and not just ophthalmology) have been Renaissance men with broad interests, but it is not clear that they made their discoveries *because* of their catholic tastes. Would not an equally tenable hypothesis be that the kind of person who is imaginative also has the capacity to be titillated by many of life's problems?

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TROPICAL SPRUE—STUDIES OF THE U. S. ARMY'S SPRUE TEAM IN PUERTO RICO. Edited by Lt. Colonel William H. Crosby, MC. Washington, D. C., 1959, Medical Science Publication No. 5, Walter Reed Army Institute of Research. Pp. 355, not indexed. Price $1.75. On sale by the Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C.

This paper-bound volume consists of twenty-five chapters comprising the selected output of the United States Army sprue team in Puerto Rico from 1953 to present. Of the twenty-five chapters nineteen have been published as articles in various journals, and have their own variable merits, but it is convenient to have them assembled between the covers of one book. The volume begins with the minutes of five yearly conferences on sprue, during which time many fascinating vignettes are disclosed of work in progress and of work begun and dropped; suggestions as to what "ought to be done" are bandied about in informal fashion. The Army was generous enough to make possible at these conferences the presence of some of the leading world authorities on various aspects of intestinal absorption, hematology, and cytology. As one might expect, there is no uniformity of treatment of the various subjects included in the panels, but for those acquainted with the field there is much fascinating interchange of ideas.

As for the nineteen chapters which constitute published papers, they deal with all phases of the sprue problem, with particular reference to tropical sprue. Some of the work has received a more orderly summary treatment by one of the members of the team, Dr. Frank Gardner, whose medical progress article, "Tropical Sprue," in the *New England Journal of Medicine*, (258:791-796, 835-842, 1958), attempts to present all phases of the problem as seen by the group in Puerto Rico and compared with studies of tropical sprue elsewhere in the world. In the course of any such discussion on tropical sprue, much information relevant to the problem of adult celiac disease or nontropical sprue also is discussed. Those skeptics who still feel that gastroenterology lags far behind other disciplines in the utilization of modern techniques will find much here to make them change their minds; the amount of ingenuity and technical prowess which has been displayed in many of these studies need not fear comparison with techniques available in any other field. Nevertheless, one cannot but feel that these are scattered and preliminary observations in an area on the surface of which we are just beginning to scratch. The book, then, although it presents no orderly point of view toward a rather well-defined disease, does put in one convenient paper-bound volume a number of widely ranging studies having to do with malabsorption in tropical climates, and allows the interested reader to learn of many new techniques being applied to gastroenterologic problems of the small intestine. It is therefore a useful contribution, although by no means a definitive one.

Albert I. Mendeloff

RESEARCH ON NOVOCAIN THERAPY IN OLD AGE. A collection of seven papers from *Die Therapiewoche*, 1956-1957, by Prof. Anna Aslan, M.D., and co-workers; Prof. C. M. Bürger, M.D., and Prof. F. H. Shulz, M.D.; and U. Köhler, M.D., and E. Mampel, M.D. New York, 1959, Consultants Bureau, Inc. Pp. 68. Price $12.50.

For those who thought that the golden age of procaine had passed, there is startling news from behind the Iron Curtain. Professor Aslan and her comrades in Bucharest run a sort of Rumanian Hoxsey Clinic, treating geriatric patients with extracts of spleen, placenta, adrenal, pineal, or thyroid; vitamin E or liquid beer yeast; or bicarbonate baths (method of Lepechinskaia). But her favorite remedy is "novocain," and why not, since it will apparently help cerebral arteriosclerosis, parkinsonism, hearing, and senile skin, turn gray hair back to its original color, or grow hair in cases of baldness?

The above tripe plus some German and Soviet hogwash along the same lines is being sold at $12.50 by an outfit called "Consultants Bureau, Inc." Now what I want to know is: For whom do these guys consult?

Louis Lasagna

PROGRESS IN ARTHRITIS. Edited by John H. Talbott, M.D., and L. Maxwell Lockie, M.D. New York, 1958, Grune & Stratton, Inc., Pp. 456. Price $12.50.

This book is presented by its eminent editors as a symposium of 27 selected subjects by different authors in the broad field of arthritis and connective tissue disorders. Emphasis and choice of topics in such a work must be a matter of individual preference, but many areas of special interest in rheumatology receive attention. One might perhaps have hoped for consideration of recent epidemiologic work in these diseases, and possibly for some mention of scientific methods in the evaluation of therapy. Similarly, many readers will wish that Dr. Ragan's authoritative discussion of serologic reactions in rheumatoid arthritis were a little less attenuated.

Mention of three chapter titles illustrates their diversity—"The Hand in Differential Diagnosis of Arthritis," "Induced Connective Tissue Syndromes," and "Arthritides of Domesticated Livestock"—the last an interesting reminder of the important role which comparative pathology may yet play in the study of connective tissue disease.

It is to be expected that some of the opinions expressed are open to question. Dr. Thompson's view that ankylosing spondylitis is merely rheumatoid arthritis of the spine is out of step with most current thought on the subject. Dr. Maxwell Lockie's account of the management of rheumatoid arthritis, though admirably detailed and supported by many years' experience, is marred by dogmatic statements of doubtful validity. It may be true that "Bed rest is absolutely essential for every patient," or that "gold salt therapy is the most effective agent in our armamentarium today to stop the progression of arthritis," but both of these hypotheses remain to be evaluated by critical therapeutic trials, and in fact urgently require such assessment.

In general, however, and despite the varying quality of the papers, the book is interesting, informative, and well produced. Not the least of its merits are the generous bibliographies.

James T. Scott

NURSING HOME MANAGEMENT. By Ralph C. Williams, B.S., M.D., Margaret Bull Armstrong, R.N., J. Fred Gunter, Edith McCulloch, R.N., and Jack Stiller. New York, 1959, F. W. Dodge Corporation. Pp. 230, indexed. Price $8.50.

Although nursing homes have become increasingly important institutions for the care of chronically ill patients, this book seems to be the first publication prepared to give direction and guidance to those concerned with the administration of these community facilities. The preface explains that, "By far the majority of those engaged in this work have had no particular training in it. For that reason, much material that may seem quite elementary to some readers has been included in the book." A person or group planning to establish a nursing home would find many helpful sources, including the officials, agencies, regulations, and laws concerned with the establishment and operation of nursing homes. For those persons already administering such institutions, the book establishes high standards of patient care which should serve as a challenge and guide for upgrading those which at present are substandard. The language of the book, its organization, and its concepts are very simple and direct.

The content is presented under the headings, "Establishment and Organization," "Business Management," "Medical and Nursing Care," "Recreational Facilities and Group Programs," "Food Service Department," "Housekeeping and Laundry Service," "Buildings and Grounds," and "Safety Program." Although the information would be helpful for those operating a fairly large institution in which each department is supervised by a specialist, it is evident that the authors are trying to be sufficiently elementary to offer assistance to all who are engaged in this work. For example, instructions are given for boiling eggs and for roasting meat. All chapters do not contain quite such detailed information, but there are many helpful schedules, charts, records, order forms, and reports illustrated throughout the book. In general the content is very appropriate to a first publication in such a field.

Whereas most of the instructions seem to be complete and very clearly stated, there are a few which would be improved by additions or revisions. In discussing the sterilization of equipment

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there is no mention made of how to handle sterile equipment to prevent contamination. Instructions state that sharp instruments are sterilized by soaking in 70 per cent alcohol, but no minimum time period is stated. Whereas instructions for food preparation are most detailed, in spite of the ready availability of cook books, there are no instructions given for such frequently used nursing procedures as bed bath, enema, and hypodermic injection or for providing adequate care for a patient with an indwelling catheter. On the other hand, the directions for providing proper body alignment, for preventing unnecessary muscle atrophy in bedfast and hemiplegic patients, and for assisting patients in self help and rehabilitation seem excellent. The chapter on safety is important in such a reference book as this.

The book has been written with the primary purpose of improving the administration of nursing homes. The needs of patients have received secondary consideration. One realizes, however, that good administration should provide high standards of care, which should in turn result in high quality of patient care, provided the staff has the warmth of personality and the very deep interest in people required for good nursing of patients in such institutions.

Myrtle Coe

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A HISTORY OF NEUROLOGY. By Walther Riese, M.D. Foreword by Félix Martí-Ibáñez, M.D. New York, 1959, MD Publications Inc. Pp. 223, indexed. Price $4.00.

This book should have been interesting. For one thing, the author is a medical historian with a long background of interest in the field. Second, Dr. Riese has held posts in well-known European universities and has apparently been trained in neurology, neuroanatomy, and physiology. Third, the author decided to avoid the often tedious chronologic approach to a whole field and to focus rather on the histories of such subsections of neurology as reflex action, cerebral localization, etc.

But the little opus never gets off the ground. Except for occasional well-made points, the writing is either turgid and impenetrable or painfully superficial. (The chapter entitled "Pain in Neurology, Ancient and Modern" is 6½ pages long, that on "The History of Prognosis in Neurology" is 2 pages long, and the one on "The History of Therapy in Neurology" is a snappy 6½ pages.)

For those readers who collect mauve nineteenth century prose, attention is directed to the foreword by the editor of this series of monographs, Dr. Martí-Ibáñez. One is tempted to quote in full the paragraph beginning at the bottom of page 7, but the reader might not believe it. Those who heard Governor Clement's keynote speech at the 1956 Democratic Convention will recognize the same ripe, fruity metaphors. Maybe Dr. Martí-Ibáñez comes from the south of Spain.

Louis Lasagna

THE DEGENERATIVE BACK AND ITS DIFFERENTIAL DIAGNOSIS. By P. R. M. J. Hanraets, M.D. Amsterdam, London, New York, and Princeton, 1959, Elsevier Publishing Co. Pp. 690.

In the course of his neurosurgical work on patients with sciatica due to protruded discs, the author became convinced that the usual concepts of back disease were too narrow. It seemed to him that the intervertebral discs played only one part and sometimes a minor one in the genesis of back disorders. This monograph is a discussion of the multiple factors which the author considers to be contributing to the back syndromes. Throughout his thesis is the thought that there is some inherent structural weakness in the bones, cartilages, ligaments, or muscles of the back which predisposes them to mechanical failure as they are subjected to the stresses of life.

To illustrate this general theme the author discusses the causes—muscular, ligamentous, congenital anomalous, osseous, and discoid—of the weak back and their relation to the general constitution of the individual and to the stresses and strains applied to the back. The major part of

the book discusses the clinical symtomatology and signs of disease of the back, with particular reference to the disc syndromes and their differential diagnosis. The final chapter concerns the conservative and surgical treatment of back disorders, mainly of disc protrusion.

The book has an extensive bibliography and an index.

There is no doubt that the author's contention that the back is subject to inherent degenera tive changes is correct. Whether all the ills which befall the vertebral column can be ascribed to such predispositions might be open to considerable argument. Practically all neurosurgeons could recite examples directly attributable to trauma, in contradistinction to the author who has not been able to find "an uncomplicated hernia nuclei pulposi in 2000 persons suffering from some form of back disorder, which could confidently be proved to have been caused by injury to a previously healthy disc." (p. 557.)

To the reviewer the argumentation of this book seemed rather lengthy for the points made. A more concise presentation might have been just as convincing and easier to read. However, the monograph presents a challenging thesis which should be of interest to every physician who has to deal with back disease.

A. Earl Walker

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DIFFUSE LESIONS OF THE STOMACH. By Ian J. Wood, M.D., F.R.C.P., F.R.A.C.P., and Leon I. Taft, M.D., B.S., B.Sc. London, 1958, Edward Arnold (Publishers) Ltd. Pp. 86. Price $6.00. The Williams & Wilkins Co., Baltimore, exclusive U. S. agents.

In this monograph the excellent pioneer work by the Melbourne group dealing with the correlation of clinical and pathologic findings in gastritis is summarized. The first section is devoted to a description of methods of investigation employed. The use of the flexible gastric biopsy tube and the preparation and staining of the specimens are described in a stepwise fashion.

The remainder of the book consists of chapters covering acute gastritis, chronic gastritis, diffuse giant hypertrophic gastritis, gastric atrophy, pernicious anemia, and subacute combined degeneration of the cord. Extensive reference is made to other studies on the subject and differences in view are pointed out. The quality of the numerous illustrations is excellent.

The authors' pathologic classification of gastritis is simpler than the one proposed by E. Palmer. In two respects their findings are at variance with Palmer's: The Melbourne group feels certain that chronic alcoholism is a common cause of chronic gastritis and that gastric atrophy may be primary and not necessarily a sequel of atrophic gastritis.

On the basis of the evidence presented Drs. Wood and Taft make a plea that gastritis be regarded as a clinical as well as a pathologic diagnosis. On the other hand, the clinical picture described sounds very much like "psychophysiologic gastrointestinal dysfunction," and only 40 per cent of their patients with biopsy-proved atrophic gastritis had symptoms, so it would seem that more has to be done to establish the correlation proposed in this monograph.

Thomas R. Hendrix

Announcements

THE NEW YORK MEDICAL COLLEGE-METROPOLITAN HOSPITAL CENTER, DEPARTMENT OF PHYSICAL MEDICINE AND REHABILITATION, announces a 2-week course at Bird S. Coler Hospital, New York, N. Y., "Principles and Practice of Geriatric Rehabilitation." For registered nurses, occupational therapists, physical therapists, and social workers, the course will be given April 25 through May 6, 1960.

It is planned to provide intensified training in the rehabilitation care of the elderly, chronically ill patient and will offer a comprehensive and practical presentation of such care in hospital, home, old-age home, and nursing home. This course will consist of lectures, seminars, clinical demonstrations, and practice workshops. The teaching staff includes members of the faculty and professional staff of the Medical Center.

The curriculum will consist of, "Physiology and Pathology of Aging," "Psychological and Social Aspects of Aging," "Clinical Conditions of the Aged," "Self-Care Activities," "Prosthetic Devices," "Nutrition and Dental Care," "Management of the Incontinent Patient," "Management of the Bedridden Patient," "Home Care Programming," and "Community Needs and Resources."

The course is supported by the United States Office of Vocational Rehabilitation and the New York State Department of Health. A limited number of Federal scholarships may be available for tuition, maintenance, and travel. Grants for New York State scholarships are available only to New York State residents or those showing evidence of intent to work in New York State.

A tuition fee of $100.00 will be charged for the course. Application should be submitted by March 1, 1960. Enrollment will be limited. For further information, write to Dr. Jerome S. Tobis, Department of Physical Medicine and Rehabilitation, New York Medical College-Metropolitan Hospital Center, New York, N. Y.

THE FIFTH INTERNATIONAL CONGRESS OF GERONTOLOGY will be held in San Francisco, Calif., Aug. 7 to 12, 1960, sponsored by the International Association of Gerontology. It is expected that between 1,500 and 2,000 persons, representing every continent, will participate in the Congress.

The program will be planned in four sections: The Biological Sciences, Clinical Medicine, Psychology and the Social Sciences, and Social Welfare. Each section will hold six scientific sessions for the presentation of papers. These four scientific sessions will meet simultaneously. Each section's program committee will be responsible for planning a general symposium to be attended by all Congress participants. In addition there will be two plenary sessions and at least one open, public meeting. In order to allow the widest possible latitude for the scientific papers, there will be no over-all Congress theme. English will be the official language for the Congress.

The basic purpose of the International Association of Gerontology is to promote the discovery, development, and dissemination of systematic knowledge concerning the aging process and the aging individual, as well as social changes and adaptations brought about by aging populations. To that end, all papers submitted should represent reports of original research in the field or systematic evaluations of operating programs. Papers which merely describe programs or practices should be of such quality that they would be acceptable for the program of any professional or scientific society.

Abstracts of the papers to be presented at the Congress must not exceed 250 words in length, should be typewritten in English, and double-spaced, with ample margins on all sides. No tabular

material shall be included in the abstracts. Four copies of each abstract should be submitted not later than Dec. 15, 1959, to the appropriate section of the Congress as indicated below. European authors will submit their abstracts to the appropriate section as set forth below.

	European Authors	All Others
Biological Sciences	Prof. James F. Danielli 182, West Hill Putney London, 15, England	Dr. Nathan W. Shock, Chief Gerontology Branch Baltimore City Hospitals Baltimore, Md., U.S.A.
Clinical Medicine	Dr. J. A. Huet 1, Place d'Iéna Paris, 16, France	Dr. Herman T. Blumenthal The Jewish Hospital 216 South Kingshighway St. Louis, Mo., U.S.A.
Psychology and the Social Sciences	Henning Friis, Director Danish National Institute of Social Research Nyhavn, 38 Copenhagen, K., Denmark	Clark Tibbitts Special Staff on Aging Department of Health, Education and Welfare Washington 25, D.C., U.S.A.
Social Welfare	Henning Friis, Director Danish National Institute of Social Research Nyhavn, 38 Copenhagen, K., Denmark	Louis Kuplan P. O. Box 2103 Sacramento 10, Calif. U.S.A.

The Congress has been granted funds which will make it possible to offer some financial assistance to those whose papers will be accepted for presentation and who will require such assistance.

There will be ample space immediately adjacent to the meeting rooms for exhibits. All inquiries relative to commercial or scientific exhibits should be addressed to Dr. Leo Gitman, Chairman, Committee on Exhibits, Brooklyn Home for the Aged, Howard and Dumont Aves., Brooklyn 12, N. Y.

The registration fee for the Congress will be $25.00 for those who register before May 31, 1960. Thereafter the registration fee will be $30.00. Forms may be obtained from Louis Kuplan, President, Fifth International Congress of Gerontology, P. O. Box 2103, Sacramento 10, Calif.

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